IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Haruhisa OGITA et al.
Serial No.: 10/594,074
Filed: September 25, 2006
For: 8-OXOADENINE COMPOUND

Art Unit: 1624
Examiner: Mark L. Berch

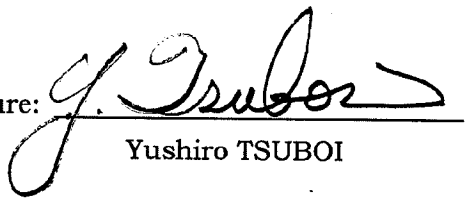
VERIFIED TRANSLATION OF PRIORITY DOCUMENT

The undersigned, of the below address, hereby certifies that he well knows both the English and Japanese languages, and that the attached is an accurate translation into the English language of the Certified Copy, filed for this application under 35 U.S.C. Section 119 and/or 365, of:

Application No.	Country	Date Filed
2004-093775	Japan	March 26, 2004

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment; or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Singed this 7th day of December, 2009

Signature: 
Yushiro TSUBOI

Address: c/o AOYAMA & PARTNERS,
IMP Building,
3-7 Shiromi 1-chome, Chuo-ku,
Osaka 540-0001 Japan

JAPAN PATENT OFFICE

This is to certify that the annexed is a true copy of the following application as filed with this Office.

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Application Number:	Patent Application No. 2004-093775
The country code and number of your priority application, to be used for filing abroad under the Paris Convention, is	JP2004-093775
Applicant(s):	Sumitomo Pharmaceuticals Co., Ltd.

Commissioner,
Japan Patent Office

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[Docket No.] 133243
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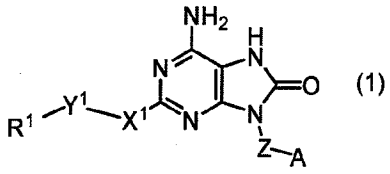
[Inventor]
[Address] c/o Sumitomo Pharmaceuticals Co., Ltd., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi
[Name] Haruhisa OGITA
[Inventor]
[Address] c/o Sumitomo Pharmaceuticals Co., Ltd., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi
[Name] Tomoaki NAKAMURA
[Inventor]
[Address] c/o Sumitomo Pharmaceuticals Co., Ltd., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi
[Name] Yoshiaki ISOBE
[Inventor]
[Address] c/o Sumitomo Pharmaceuticals Co., Ltd., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi
[Name] Kazuki HASHIMOTO
[Inventor]
[Address] c/o Sumitomo Pharmaceuticals Co., Ltd., 1-98, Kasugadenaka 3-chome, Konohana-ku, Osaka-shi
[Name] Ayumu KURIMOTO
[Applicant]
[Identification No.] 000183370
[Name] Sumitomo Pharmaceuticals Co., Ltd.
[Agent]
[Identification No.] 100121588
[Patent Attorney]
[Name] Yutaka ISOBE
[Phone] 06-6466-5214
[Payment of Fees]
[Prepayment Book No.] 056546
[Amount to be paid] 21,000 yen
[Attached Documents]
[Item] Claims 1
[Item] Specification 1
[Item] Abstract 1
[Number of General Power of Attorney] 0205876

[Document Name] Claims

[Claim 1]

An 8-oxoadenine compound represented by the following formula (1):

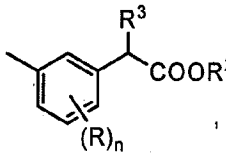
[Chemical formula 1]



(1)

[wherein "-A" is a group selected from the group consisting of the following formulas (2) to (8):

[Chemical formula 2]



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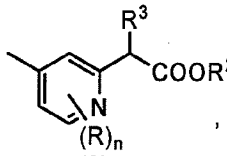

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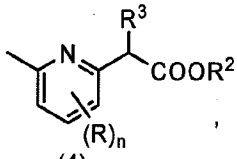

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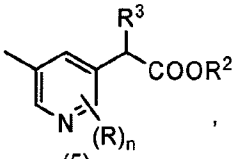

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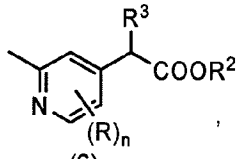

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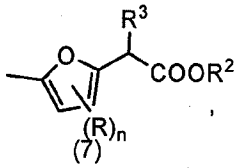

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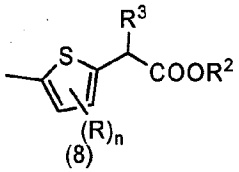


(8)

(wherein R^2 is a substituted or unsubstituted alkyl group; R^3 is hydrogen atom or an alkyl group; R is a halogen atom, a haloalkyl group, an alkyl group, an alkoxy group, an haloalkoxy group, amino group, an alkylamino group or a dialkylamino group; n is an integer of 0 to 2, and when n is 2, R may be the same or different);

X^1 is oxygen atom, sulfur atom, SO_2, NR^4 (R^4 is hydrogen atom or an alkyl group), or a single bond;

Y^1 is a single bond or a straight or branched chain alkylene;

Z is a straight or branched chain alkylene;

R^1 is hydrogen atom, hydroxy group, an alkoxy group, an alkylthio group, a substituted or unsubstituted alkoxycarbonyl group, an alkylsulfonyl group, a haloalkoxy group, amino group, an alkylamino group, a dialkylamino group, a cyclic amino group, carbamoyl group, an alkylcarbamoyl group, a dialkyl-carbamoyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted cycloalkyl

group]
or a pharmaceutically acceptable salt thereof.

[Claim 2] The 8-oxoadenine compound or a pharmaceutically acceptable salt according to claim 1, wherein R^2 in the formula (1) is a methyl group.

[Claim 3] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to claim 1 or 2, wherein R^3 in the formula (1) is a hydrogen atom.

[Claim 4] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 3, wherein Z in the formula (1) is a straight chain C_{1-5} alkylene.

[Claim 5] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 4, wherein X^1 in the formula (1) is a single bond, oxygen atom or sulfur atom.

[Claim 6] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 5, wherein Y^1 in the formula (1) is a straight chain C_{1-6} alkylene.

[Claim 7] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to any one of claims 1 to 6, wherein R^1 in the formula (1) is hydrogen atom, an alkoxycarbonyl group, hydroxy group, or an alkoxy group.

[Claim 8] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to claim 1, wherein X^1 in the formula (1) is a single bond, Y^1 is a straight chain C_{1-6} alkylene, and R^1 is methoxycarbonyl group.

[Claim 9] A pharmaceutical composition comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

[Claim 10] An immuno-modulator comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

[Claim 11] A therapeutic or prophylactic agent for viral diseases comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

[Claim 12] A therapeutic or prophylactic agent for allergic diseases comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

[Claim 13] A therapeutic or prophylactic agent for cancers comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

[Claim 14] A pharmaceutical composition for topical administration comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

[Document Name] Description

[Title of Invention] 8-Oxoadenine compound

[Technical Field]

[0001]

The present invention relates to a novel 8-oxoadenine compound being useful as a therapeutic or prophylactic agent for allergic diseases, viral diseases or cancers.

[Background Art]

[0002]

Interferon is an endogenous protein having an important role in an immune system in mammals, and not only takes a partial role in a nonspecific defense mechanism in a living body but also strongly participates in a specific defense mechanism thereof. Actually, interferon has been used as an agent for treating viral diseases such as hepatitis B and hepatitis C in the clinical field. A low molecular weight organic compound which induces a biosynthesis of said interferon (an interferon-inducing agent) has been developed as the next generation interferon therapy, including an imidazoquinoline derivative (refer to Patent Document 1) and an adenine derivative (refer to Patent Documents 2 and 3), etc., and an imidazoquinoline derivative, Imiquimod, has been used as an external antiviral agent for genital wart in the clinical field.

On the other hand, T-cell taking a central role in an immune response in a living body is classified into two groups, Th1-cell and Th2-cell, and in a living body of a patient suffering from an allergic disease, an excess amount of cytokines such as interleukin-4 (IL-4) and interleukin-5 (IL-5) is excreted from Th-2 cell, and thus a compound suppressing an immune response of Th2 cell can be expected as an agent for treating allergic diseases.

The above imidazoquinoline derivative and adenine derivative have been known to show a suppressing activity of production of interleukin-4 (IL-4) and interleukin-5 (IL-5) as well as an inducing activity of interferon, and they have been actually known to be effective to an allergic disease in an animal model.

However, there is such a fear that systemic adverse effects based on the interferon inducing activity would be problem upon using such derivatives as an anti-allergic agent.

[Patent Document 1] US Patent 4,689,338

[Patent Document 2] WO 98/01448

[Patent Document 3] WO 99/28321

[DISCLOSURE OF INVENTION]

[Problems to be solved by Invention]

[0003]

The problem to be solved by the present invention is to provide an immuno-modulator having specific activity against Th1/Th2, preferably a medicament for topical application which is characterized by preventing the

systemic adverse effects based on the interferon inducing activity. That is, the present invention is to provide a novel 8-oxoadenine compound which is quickly metabolized to convert into a low-active compound when topically administered, and a medicament for topical application as a therapeutic or prophylactic agent with the reduced systemic pharmacological activity for allergic diseases, viral diseases and cancers, comprising the said compound as the active ingredient.

[Means for solving the problems]

[0004]

The present inventors have made extensive study for obtaining a therapeutic or prophylactic agent for immune diseases such as allergic diseases, viral diseases and cancers, which shows potent effect at the administered site and does not show the systemic adverse effects when externally administered in a form of aerosols, etc., being effective in diseases such as asthma, and found the 8-oxoadenine compound of the present invention. Namely, the compound of the present invention is useful as a therapeutic or prophylactic agent for allergic diseases, viral diseases and cancers with the reduced systemic pharmacological activity. Thus, the prevent invention has been accomplished on the basis of the above finding.

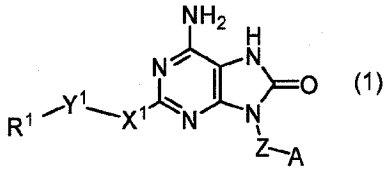
[0005]

The present invention is as follows:

[1] An 8-oxoadenine compound represented by the following formula (1):

[0006]

[Chemical formula 1]

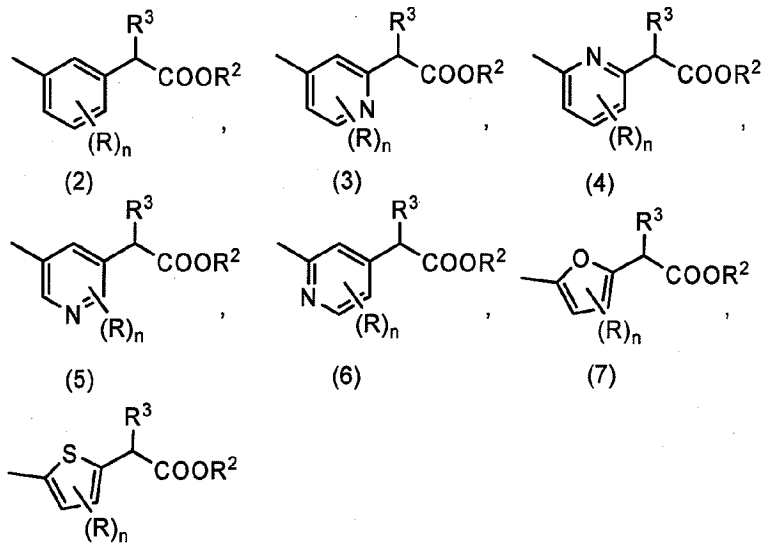


(1)

[wherein "-A" is a group selected from the group consisting of the following formulas (2) to (8):

[0007]

[Chemical formula 2]



(2) (3) (4)

(5) (6) (7)

(8)

(wherein R^2 is a substituted or unsubstituted alkyl group; R^3 is hydrogen atom or an alkyl group; R is a halogen atom, a haloalkyl group, an alkyl group, an alkoxy group, an haloalkoxy group, amino group, an alkylamino group or a dialkylamino group; n is an integer of 0 to 2, and when n is 2, R may be the same or different); X^1 is oxygen atom, sulfur atom, SO_2, NR^4 (R^4 is hydrogen atom or an alkyl group), or a single bond;

Y^1 is a single bond or a straight or branched chain alkylene;

Z is a straight or branched chain alkylene;

R^1 is hydrogen atom, hydroxy group, an alkoxy group, an alkylthio group, a substituted or unsubstituted alkoxycarbonyl group, an alkylsulfonyl group, a haloalkoxy group, amino group, an alkylamino group, a dialkylamino group, a cyclic amino group, carbamoyl group, an alkylcarbamoyl group, a dialkylcarbamoyl group, a substituted or unsubstituted aryl group, a substituted or unsubstituted heteroaryl group, or a substituted or unsubstituted cycloalkyl group]

or a pharmaceutically acceptable salt thereof.

[2] The 8-oxoadenine compound or a pharmaceutically acceptable salt as described in [1], wherein R^2 in the formula (1) is a methyl group.

[3] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1] or [2], wherein R^3 in the formula (1) is hydrogen atom.

[4] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in any one of [1] to [3], wherein Z in the formula (1) is a straight chain C_{1-5} alkylene.

[5] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in any one of [1] to [4], wherein X^1 in the formula (1) is a single bond, oxygen atom or sulfur atom.

[6] The 8-oxoadenine compound or a pharmaceutically acceptable salt

thereof as described in any one of [1] to [5], wherein Y^1 in the formula (1) is a straight chain C_{1-6} alkylene.

[7] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in any one of [1] to [6], wherein R^1 in the formula (1) is hydrogen atom, an alkoxycarbonyl group, hydroxy group, or an alkoxy group.

[8] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1], wherein in the formula (1) X^1 is a single bond, Y^1 is a straight chain C_{1-6} alkylene, and R^1 is methoxycarbonyl group.

[9] A pharmaceutical composition comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of [1] to [8] as the active ingredient.

[10] An immuno-modulator comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of [1] to [8] as the active ingredient.

[11] A therapeutic or prophylactic agent for viral diseases comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of [1] to [8] as the active ingredient.

[12] A therapeutic or prophylactic agent for allergic diseases comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of [1] to [8] as the active ingredient.

[13] A therapeutic or prophylactic agent for cancers comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of claims 1 to 8 as the active ingredient.

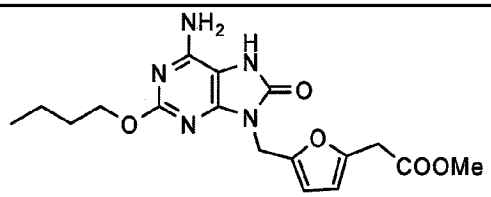
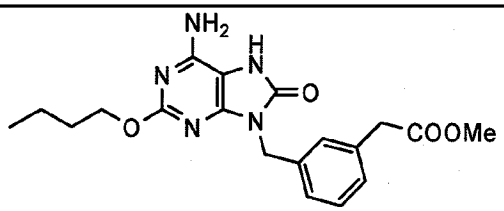
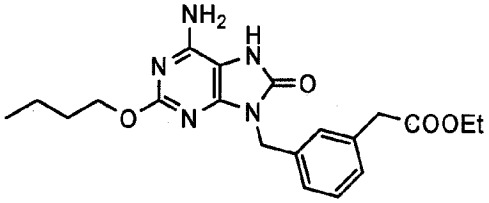
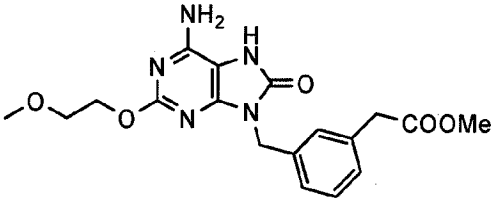
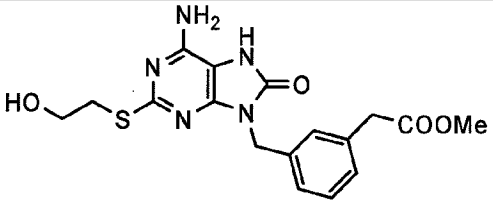
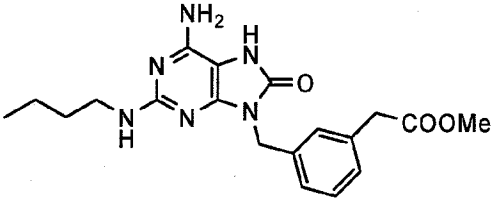
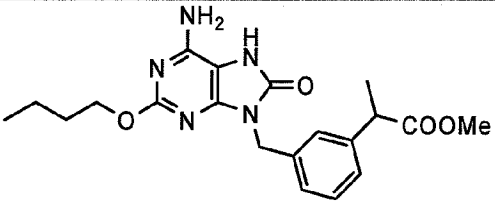
[14] A pharmaceutical composition for topical administration comprising the 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as set forth in any one of [1] to [8] as the active ingredient.

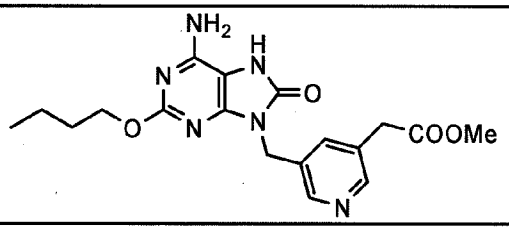
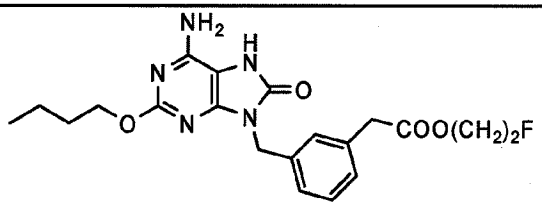
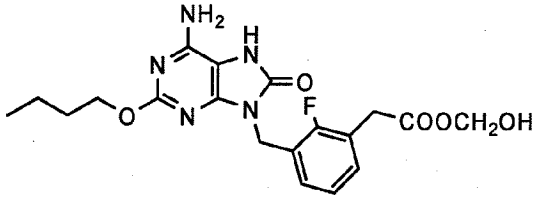
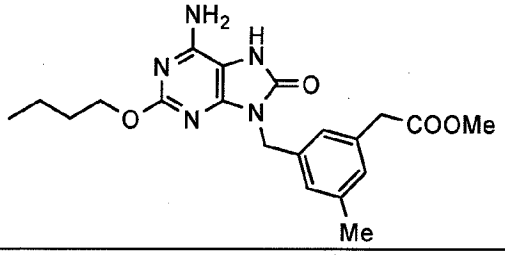
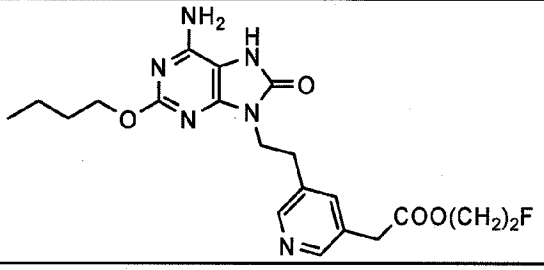
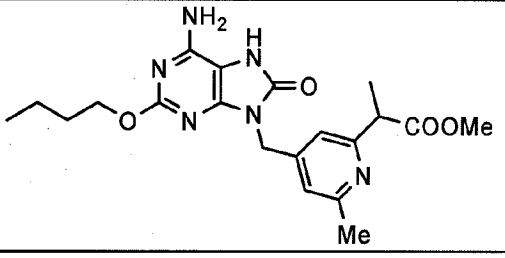
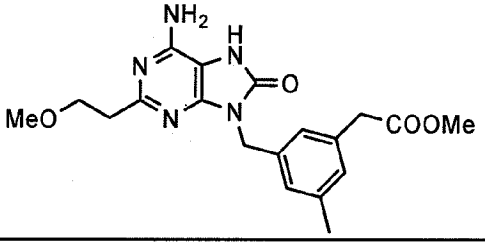
[0008]

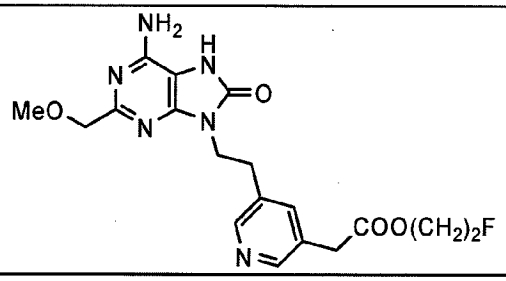
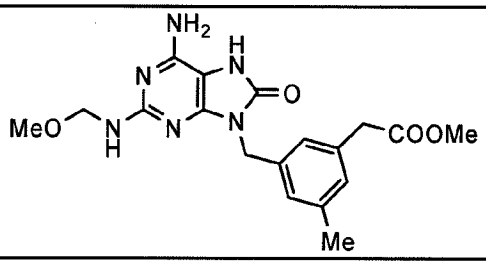
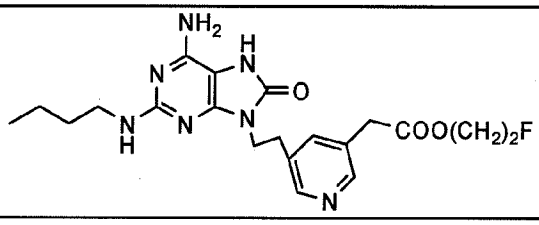
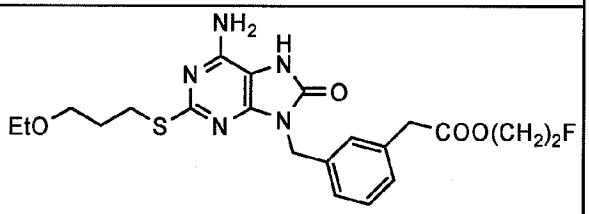
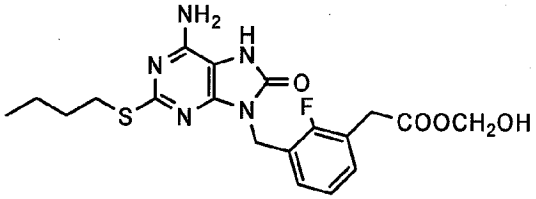
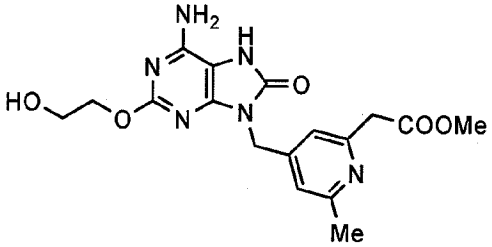
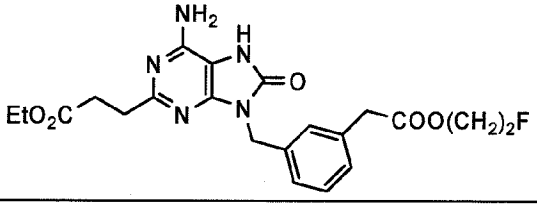
[15] An 8-oxoadenine compound or a pharmaceutically acceptable salt thereof according to any one of [1] to [8], provided that the compounds mentioned in the following Table 1 are excluded.

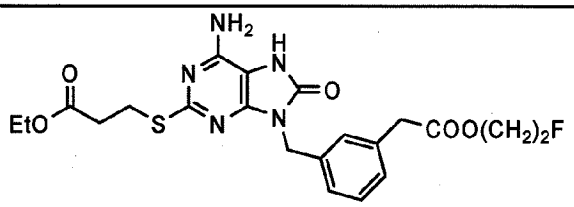
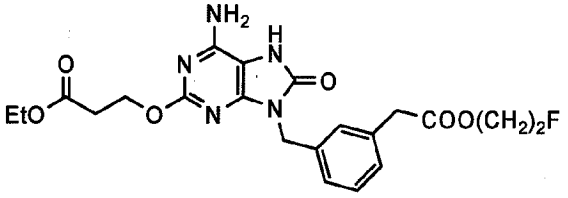
[0009]

[Table 1]

Compound	Structure
2-Butoxy-9-(5-methoxycarbonyl-methylfurfuryl)-8-oxoadenine	
2-Butoxy-9-(3-methoxycarbonyl-methylbenzyl)-8-oxoadenine	
2-Butoxy-9-(3-ethoxycarbonyl-methylbenzyl)-8-oxoadenine	
9-(3-Methoxycarbonylmethyl-benzyl)-2-(2-methoxyethoxy)-8-oxoadenine	
2-(2-Hydroxyethylthio)-9-(3-methoxycarbonylmethyl benzyl)-8-oxoadenine	
2-Butylamino-9-(3-methoxy-carbonylmethylbenzyl)-8-oxoadenine	
2-Butoxy-9-{3-((1R,S)-1-methoxy-carbonylethyl)benzyl}-8-oxoadenine	

2-Butoxy-9-{(5-methoxycarbonyl-methyl-3-pyridyl)methyl}-8-oxoadenine	
2-Butoxy-9-{3-(2-fluoroethoxy-carbonylmethyl)benzyl}-8-oxoadenine	
2-Butoxy-9-{2-fluoro-3-(hydroxy-methyloxycarbonylmethyl)benzyl} -8-oxoadenine	
2-Butoxy-9-{3-(methoxycarbonyl-methyl)-5-methylbenzyl}-8-oxoadenine	
2-Butoxy-9-[2-{5-(2-fluoroethoxy-carbonylmethyl)-3-pyridyl}ethyl]-8-oxoadenine	
2-Butoxy-9-{2-methyl-6-(1-methoxycarbonylethyl)-4-pyridylmethyl}-8-oxoadenine	
2-(2-Methoxyethyl)-9-{3-(methoxycarbonylmethyl)-5-methylbenzyl}-8-oxoadenine	

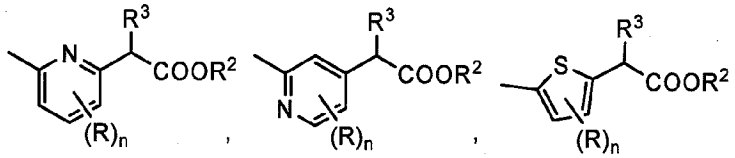
2-Methoxymethyl-9-[2-{5-(2-fluoroethoxycarbonylmethyl)-3-pyridyl}ethyl]-8-oxoadenine	
2-Methoxymethylamino-9-(5-methyl-3-methoxycarbonylmethylbenzyl)-8-oxoadenine	
2-Butylamino-9-[2-{5-(2-fluoroethoxycarbonylmethyl)-3-pyridyl}ethyl]-8-oxoadenine	
2-(3-Ethoxypropylthio)-9-{3-(2-fluoroethoxycarbonylmethyl)-benzyl}-8-oxoadenine	
2-Butylthio-9-(2-fluoro-3-hydroxymethyloxycarbonylmethylbenzyl)-8-oxoadenine	
2-(2-Hydroxyethoxy)-9-(6-methyl-2-methoxycarbonylmethyl-4-pyridylmethyl)-8-oxoadenine	
2-(2-Ethoxycarbonyl)ethyl-9-{3-(2-fluoroethoxycarbonylmethyl)-benzyl}-8-oxoadenine	

2-(2-Ethoxycarbonylethylthio)-9-{3-(2-fluoroethoxycarbonyl-methyl)benzyl}-8-oxoadenine	
2-(2-Ethoxycarbonylethoxy)-9-{3-(2-fluoroethoxycarbonylmethyl) benzyl}-8-oxoadenine	

[16] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1], wherein "-A" in the formula (1) is a group of the formula (4), the formula (6) or the formula (8):

[0010]

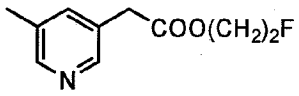
[Chemical formula 3]



(4) (6) (8)

(wherein n, R^2 and R^3 are the same as defined above).

[17] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1], wherein Z in the formula (1) is a straight chain C_{2-5} alkylene, provided that the group of "-A" is not a group of the formula (9):

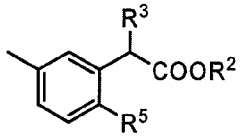


(9)

[18] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1], wherein "-A" in the formula (1) is a group represented by the formula (10):

[0011]

[Chemical formula 4]



(10)

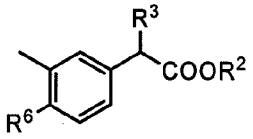
(wherein R^2 and R^3 are the same as defined above and R^5 is a halogen atom or an alkoxy group).

[19] The 8-oxoadenine compound or a pharmaceutically acceptable salt

thereof as described in [1], wherein "-A" in the formula (1) is a group represented by the formula (11):

[0012]

[Chemical formula 4]



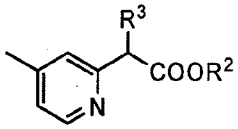
(11)

(wherein R^2 and R^3 are the same as defined above and R^6 is a halogen atom or an alkoxy group).

[20] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1], wherein "-A" in the formula (1) is a group represented by the formula (12):

[0013]

[Chemical formula 6]



(12)

(wherein R^2 and R^3 are the same as defined above).

[21] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [1], wherein R^1 in the formula (1) is an alkoxycarbonyl group, excluding the compounds wherein R^2 is 2-fluoroethyl group, Y^1 is ethylene and R^1 is ethoxycarbonyl group.

[22] The 8-oxoadenine compound or a pharmaceutically acceptable salt thereof as described in [21], wherein X^1 is a single bond.

[Effects of Invention]

[0014]

The present invention is to provide an adenine compound being useful as a medicament for topical application, which is characterized of exhibiting its drug efficacy at the administered site and exhibiting no systemically pharmacological effects. By the present invention, it becomes possible to treat or prevent allergic diseases such as asthma and atopic dermatitis, and viral diseases such as herpes, etc.

[Best Mode for Carrying out the Invention]

[0015]

Hereinafter, the embodiments of the present invention are illustrated in detail.

The "halogen atom" in the present specification is exemplified by fluorine,

chlorine, bromine or iodine, preferably fluorine or chlorine.

[0016]

The "alkyl group" is exemplified by a straight or branched chain C_{1-10} alkyl group, including specifically methyl group, ethyl group, propyl group, 1-methylethyl group, butyl group, 2-methylpropyl group, 1-methylpropyl group, 1,1-dimethylethyl group, pentyl group, 3-methylbutyl group, 2-methylbutyl group, 2,2-dimethylpropyl group, 1-ethylpropyl group, 1,1-dimethylpropyl group, hexyl group, 4-methylpentyl group, 3-methylpentyl group, 2-methylpentyl group, 1-methylpentyl group, 3,3-dimethylbutyl group, 2,2-dimethylbutyl group, 1,1-dimethylbutyl group, 1,2-dimethylbutyl group, heptyl group, 1-methylhexyl group, 1-ethylpentyl group, octyl group, 1-methylheptyl group, 2-ethylhexyl group, nonyl group, and decyl group, and preferably an C_1-C_6 alkyl group, more preferably an C_1-C_4 alkyl group.

[0017]

The "cycloalkyl group" is exemplified by a 3- to 8-membered monocyclic cycloalkyl group, including specifically cyclopropyl group, cyclobutyl group, cyclopentyl group, cycloheptyl group, and cyclooctyl group.

[0018]

The "alkylene" is exemplified by a straight or branched chain C_1-C_6 alkylene, including specifically methylene, ethylene, trimethylene, tetramethylene, pentamethylene, hexamethylene, 1-methylmethylene, 1-ethylmethylene, 1-propylmethylene, 1-methylethylene, 2-methylethylene, 1-methyltrimethylene, 2-methyltrimethylene, 2-methyltetramethylene, and 3-methylpentamethylene.

[0019]

The "alkoxy group" is exemplified by a straight or branched chain C_1-C_{10} alkoxy group, including specifically methoxy group, ethoxy group, propoxy group, 1-methylethoxy group, butoxy group, 2-methylpropoxy group, 1-methylpropoxy group, 1,1-dimethylethoxy group, pentoxy group, 3-methylbutoxy group, 2-methylbutoxy group, 2,2-dimethylpropoxy group, 1-ethylpropoxy group, 1,1-dimethylpropoxy group, hexyloxy group, 4-methylpentyloxy group, 3-methylpentyloxy group, 2-methylpentyloxy group, 1-methylpentyloxy group, 3,3-dimethylbutoxy group, 2,2-dimethylbutoxy group, 1,1-dimethylbutoxy group, 1,2-dimethylbutoxy group, heptyloxy group, 1-methylhexyloxy group, 1-ethylpentyloxy group, octyloxy group, 1-methylheptyloxy group, 2-ethylhexyloxy group, nonyloxy group, and decyloxy group, and preferably an C_1-C_6 alkoxy group, more preferably an C_1-C_4 alkoxy group.

[0020]

The "alkylthio group" is exemplified by a straight or branched chain C_1-C_{10} alkylthio group, including specifically methylthio group, ethylthio group, propylthio group, 1-methylethylthio group, butylthio group, 2-methylpropylthio group, 1-methylpropylthio group, 1,1-dimethylethylthio group, pentylthio group, 3-methylbutylthio group, 2-methylbutylthio group, 2,2-dimethylpropylthio group,

1-ethylpropylthio group, 1,1-dimethylpropylthio group, hexylthio group, 4-methylpentylthio group, 3-methylpentylthio group, 2-methylpentylthio group, 1-methylpentylthio group, 3,3-dimethylbutylthio group, 2,2-dimethylbutylthio group, 1,1-dimethylbutylthio group, 1,2-dimethylbutylthio group, heptylthio group, 1-methylhexylthio group, 1-ethylpentylthio group, octylthio group, 1-methylheptylthio group, 2-ethylhexylthio group, nonylthio group, or decylthio group, preferably an C_1-C_6 alkylthio group, more preferably an C_1-C_4 alkylthio group.

[0021]

The "alkoxy" in the "alkoxycarbonyl group" is the same as the above-mentioned alkoxy group. The alkoxycarbonyl group is exemplified by a straight or branched chain C_2-C_5 alkoxycarbonyl group, including specifically methoxycarbonyl group, ethoxycarbonyl group, propoxycarbonyl group, 2-methylethoxycarbonyl group, butoxycarbonyl group and 2-methylpropoxy-carbonyl group.

[0022]

The "alkyl" in the "alkylsulfonyl group" is the same as the above-mentioned alkyl group. The alkylsulfonyl group is preferably exemplified by a straight or branched chain C_1-C_4 alkylamino group, including specifically methanesulfonyl group, ethanesulfonyl group, propylsulfonyl group, 2-methyl-ethylsulfonyl group and butylsulfonyl group.

[0023]

The "alkyl" in the "alkylamino group" is the same as the above-mentioned alkyl group. The alkylamino group is preferably exemplified by a straight or branched chain C_1-C_4 alkylamino group, including specifically methylamino group, ethylamino group, propylamino group, 2-methylethylamino group and butylamino group.

The two alkyls in the "dialkylamino group" may be the same or different and the "alkyl" is the same as the above-mentioned alkyl group. The dialkyl-amino group is preferably exemplified by a straight or branched chain C_1-C_4 dialkylamino group, including specifically dimethylamino group, diethylamino group, dipropylamino group, methylethylamino group, methylpropylamino group and ethylpropylamino group.

The "cyclic amino group" is preferably exemplified by a 4- to 7-membered saturated cyclic amino group containing 1 to 2 heteroatom(s) selected from 1 to 2 nitrogen atom(s), 0 to 1 oxygen atom and 0 to 1 sulfur atom, including specifically azetidinyl group, piperidinyl group, piperazinyl group, morpholino group and thiomorpholino group.

[0024]

The "alkyl" in the "alkylcarbamoyl group" is the same as the above-mentioned alkyl group. The alkylcarbamoyl group is preferably exemplified by a straight or branched chain C_{1-4} alkylcarbamoyl group, including specifically

methylcarbamoyl group, ethylcarbamoyl group, propylcarbamoyl group, 2-methylethylcarbamoyl group and butylcarbamoyl group.

The two alkyls in the "dialkylcarbamoyl group" may be the same or different and the "alkyl" is the same as the above-mentioned alkyl group. The dialkylcarbamoyl group is preferably exemplified by a straight or branched chain C_{1-4} dialkylcarbamoyl group, including specifically dimethylcarbamoyl group, diethylcarbamoyl group, and methylethylcarbamoyl group.

[0025]

The "haloalkyl group" is exemplified by an alkyl group substituted by the same or different 1-5 halogen atom(s), including specifically trifluoromethyl group, 2,2,2-trifluoroethyl group, 2,2-difluoroethyl group and pentafluoroethyl group.

The "haloalkoxy group" is exemplified by an alkoxy group substituted by the same or different 1-5 halogen atom(s), including specifically trifluoromethoxy group, 2,2,2-trifluoroethoxy group, 2,2-difluoroethoxy group and pentafluoro-ethoxy group.

[0026]

The "aryl group" is exemplified by phenyl group, 1-naphthyl group or 2-naphthyl group.

The "heteroaryl group" is exemplified by a 5- to 10-membered monocyclic or bicyclic heteroaryl group containing 1-3 hetero atom(s) selected from 0-2 nitrogen atom(s), 0-1 oxygen atom and 0-1 sulfur atom, including specifically furyl group, thienyl group, pyrrolyl group, pyridyl group, indolyl group, isoindolyl group, quinolyl group, isoquinolyl group, pyrazolyl group, imidazolyl group, pyrimidinyl group, pyrazinyl group, pyridazinyl group, thiazolyl group and oxazolyl group.

[0027]

When the alkyl and alkoxycarbonyl groups in the present specification are substituted, the substituents include a halogen atom, hydroxy group, an alkoxy group, an acyloxy group, a dialkylamino group, an aryl group, a heteroaryl group, etc.

The above-mentioned acyloxy group includes an C_2-C_6 alkylcarbonyloxy group, an arylcarbonyloxy group, or a heteroarylcarbonyloxy group. The "alkyl" in the above-mentioned alkylcarbonyloxy group is the same as the above-mentioned alkyl group. The "aryl" in the above-mentioned arylcarbonyloxy group is the same as the above-mentioned aryl group. The "heteroaryl" in the above-mentioned heteroarylcarbonyloxy group is the same as the above-mentioned heteroaryl group.

[0028]

When the aryl, heteroaryl and cycloalkyl groups in the present specification are substituted, the substituents include a halogen atom, hydroxy group, an alkyl group, an alkoxy group, a haloalkyl group, a haloalkoxy group,

an amino group, an alkylamino group, a dialkylamino group, etc.

[0029]

The "-A" in the formula (1) is preferably the group represented by the formula (2), the formula (3), the formula (4), the formula (7) or the formula (8) as mentioned above, more preferably the group represented by the formula (2), the formula (7) or the formula (8).

[0030]

In the formulas (2) to (8), R is preferably fluorine, chlorine, methyl group, ethyl group, methoxy group, ethoxy group, trifluoromethyl group, trifluoromethoxy group and dimethylamino group.

In the formulas (2) to (8), n is preferably 0 or 1.

In the formulas (2) to (8), R^2 is preferably a C_1-C_4 alkyl group or a C_3-C_8 acyloxyalkyl group. The above-mentioned acyloxyalkyl group includes acetoxymethyl group, 1-acetoxyethyl group and benzoyloxymethyl. More preferably, R^2 is methyl group.

In the formulas (2) to (8), R^3 is preferably hydrogen atom or methyl group, and more preferably hydrogen atom.

[0031]

In the formula (1), Z is preferably a straight or branched C_1-C_5 alkylene, more preferably a straight chain C_1-C_5 alkylene, including methylene, ethylene, propylene, butylene, or pentynylene, and further preferably a C_1-C_3 alkylene.

[0032]

When X^1 in the formula (1) is NR^4, R^4 is preferably hydrogen atom or an C_1-C_3 alkyl group, more preferably hydrogen atom or methyl group. X^1 is preferably a single bond or oxygen atom.

In the formula (1), the "alkylene" for Y^1 is a C_1-C_6 alkylene, including methylene, ethylene, trimethylene, tetramethylene, pentamethylene, methylmethylene, dimethylmethylene, 1-methylethylene, 2-methylethylene, 1-methyltrimethylene, 2-methyltetramethylene, or 3-methyltrimethylene. Y^1 is preferably a straight chain C_1-C_4 alkylene.

[0033]

When the alkoxycarbonyl group for R^1 in the formula (1) is substituted, the substituents include a halogen atom, hydroxy group, an C_1-C_4 alkoxy group, an C_2-C_5 alkylcarbonyloxy group, benzoyloxy group, phenyl group or pyridyl group, etc.

[0034]

R^1 is preferably hydrogen atom, hydroxy group, a straight or branched chain C_1-C_4 alkoxy group, a straight or branched chain C_1-C_4 alkylthio group, a straight or branched chain C_2-C_5 alkoxycarbonyl group, a straight or branched chain C_1-C_4 alkylsulfonyl group, amino group, a straight or branched chain C_1-C_4 alkylamino group, a straight or branched chain C_1-C_4 dialkylamino group, a C_1-C_2 haloalkyl group, a haloalkoxy group, morpholino group, 1-piperazinyl group,

1-pyrrolidinyl group, phenyl group, or pyridyl group. More preferably R^1 is hydrogen atom, hydroxy group, a straight or branched chain C_1-C_4 alkoxy group, or a straight or branched chain C_2-C_5 alkoxycarbonyl group.

The above-mentioned alkoxy group includes methoxy group, ethoxy group, propoxy group, etc. The above-mentioned alkoxycarbonyl group includes methoxycarbonyl group, ethoxycarbonyl group, etc. The above-mentioned haloalkyl group includes trifluoromethyl group, etc. The above-mentioned haloalkoxy group includes trifluoromethoxy group, etc.

[0035]

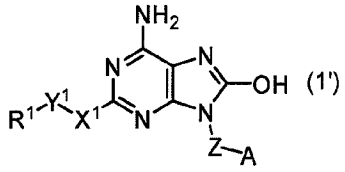
The adenine compound of the present invention includes all tautomers, geometrical isomers and stereoisomers which are formed in accordance with the kind of the substituent, and a mixture thereof.

Namely, in a case where there are one or more asymmetrical carbon atoms in the compound of the formula (1), there exist diastereomers and optical isomers, and mixtures of those diastereomers and optical isomers and separated ones are also included in the present invention.

Additionally, the adenine compound shown by the formula (1) and its tautomer are chemically equivalent, and the adenine compound of the present invention includes such a tautomer. Such tautomer is specifically a hydroxy compound shown by the formula (1'):

[0036]

[Chemical formula 7]



(wherein "-A", X^1, Y^1, Z and R^1 are the same as define above).

[0037]

The pharmaceutically acceptable salt is exemplified by an acid addition salt and a base addition salt. The acid addition salt is, for example, an inorganic acid salt such as hydrochloride, hydrobromide, sulfate, hydroiodide, nitrate and phosphate, and an organic acid salt such as citrate, oxalate, acetate, formate, propionate, benzoate, trifluoroacetate, maleate, tartrate, methanesulfonate, benzenesulfonate and p-toluenesulfonate, and the base addition salt is exemplified by an inorganic base salt such as sodium salt, potassium salt, calcium salt, magnesium salt and ammonium salt, and an organic base salt such as triethylammonium salt, triethanolammonium salt, pyridinium salt and diisopropylammonium salt, and further a basic or acidic amino acid salt such as arginine salt, aspartic acid salt and glutamic acid salt are also included. The compound shown by the formula (1) may be a hydrate or a solvate such as ethanolate.

[0038]

The compound shown by the formula (1) can be prepared by the following methods. The starting compounds which are not disclosed below can be prepared by a similar method to the following methods or by a known method or its similar method.

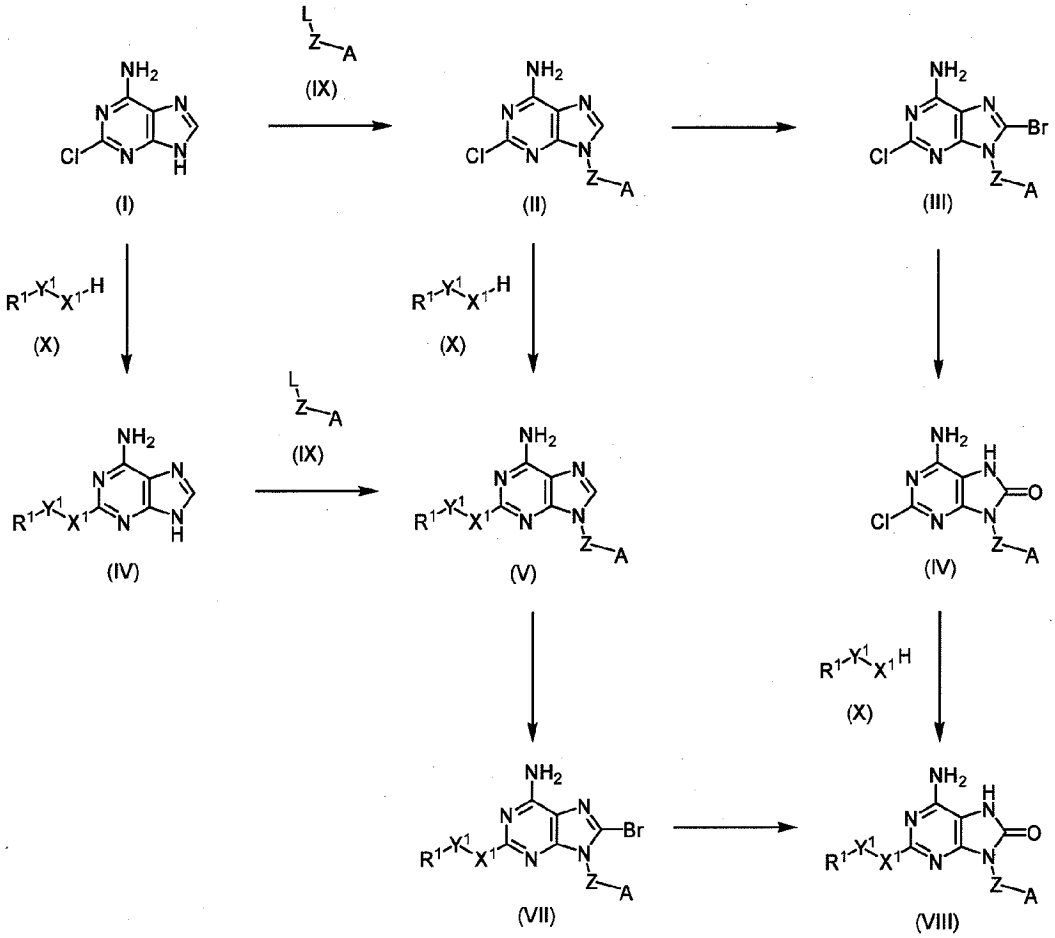
[0039]

The compound shown by the formula (1) can be prepared by the following methods. The starting compounds which are not disclosed below can be prepared by a similar method to the following methods or by a known method or its similar method.

Preparation method 1

[0040]

[Chemical formula 8]



(wherein L is a leaving group, A, R^1, X^1, Y^1 and Z are same as defined above).

The compound (II) can be prepared by reacting the compound (I) and the compound (IX) in the presence of a base.

The base includes an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium

carbonate, a metal hydroxide such as sodium hydroxide or potassium hydroxide, or a metal hydride such as sodium hydride, or a metal alkoxide such as potassium t-butoxide. The solvent includes a halogenated hydrocarbon such as carbon tetrachloride, chloroform or methylene chloride, an ether such as diethyl ether, tetrahydrofuran, or 1,4-dioxane, an aprotic solvent such as dimethylformamide, dimethylsulfoxide, or acetonitrile. The reaction temperature is selected from a range of about 0°C to around the boiling point of the solvent.

[0041]

The compound (III) can be prepared by brominating the compound (II). The brominating agent includes bromine, hydrobromic acid, perbromide, or N-bromosuccimide. In this reaction, a reaction auxiliary such as sodium acetate may be added. The solvent includes, for example, halogenated hydrocarbon such as carbon tetrachloride, ethylene chloride or dichloroethane, an ether such as diethyl ether, acetic acid, or carbon disulfide. The reaction temperature is selected from a range of about 0°C to around the boiling point of the solvent.

[0042]

The compound (VI) can be prepared by reacting the compound (III) and a metal alkoxide such as sodium methoxide, followed by treating the resultant under acidic conditions.

The solvents used in reacting with a metal alkoxide include an ether such as diethyl ether, tetrahydrofuran or 1,4-dioxane, an aprotic solvent such as dimethylformamide, or an alcohol corresponding to a metal alkoxide such as methanol used. The reaction temperature is selected from a range of room temperature to around the boiling point of the solvent.

The acid used in the acid-treatment includes an inorganic acid such as hydrochloric acid, hydrobromic acid or sulfuric acid, or an organic acid such as trifluoroacetic acid. The solvent includes, for example, water or a mixture of water and an organic solvent. The above-mentioned organic solvent includes an ether such as diethyl ether or tetrahydrofuran, an aprotic solvent such as dimethylformamide or acetonitrile, or an alcohol such as methanol or ethanol. The reaction temperature is selected from a range of room temperature to around the boiling point of the solvent.

[0043]

The compound (VIII) can be prepared by reacting the compound (IV) and the compound (X).

When X^1 is NR^4, the reaction is carried out in the presence or absence of a base. The base includes an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, a metal hydroxide such as sodium hydroxide or potassium hydroxide, or an organic base such as triethylamine, diisopropylethylamine or 4-dimethylaminopyridine. The solvent includes, for example, an ether such as tetrahydrofuran, 1,4-dioxane or diglyme, an alcohol such as propanol or butanol, or an

aprotic solvent such as dimethylformamide. The reaction may be carried out without a solvent. The reaction temperature is selected from a range of about 50°C to 200°C.

When X^1 is oxygen atom or sulfur atom, the reaction is carried out in the presence of a base. The base includes, for example, an alkali metal such as sodium or potassium, an alkali metal hydride such as sodium hydride. The solvent includes, for example, an ether such as tetrahydrofuran, 1,4-dioxane or diglyme, or an aprotic solvent such as dimethylformamide or dimethylsulfoxide. Alternatively, the reaction may be carried out without a solvent. The reaction temperature is selected from a range of about 50°C to 200°C.

In addition, the compound wherein X^1 is SO_2 can be obtained by oxidizing the intermediate compound wherein the corresponding X^1 is sulfur atom with Oxone or m-chloroperbenzoic acid (m-CPBA).

[0044]

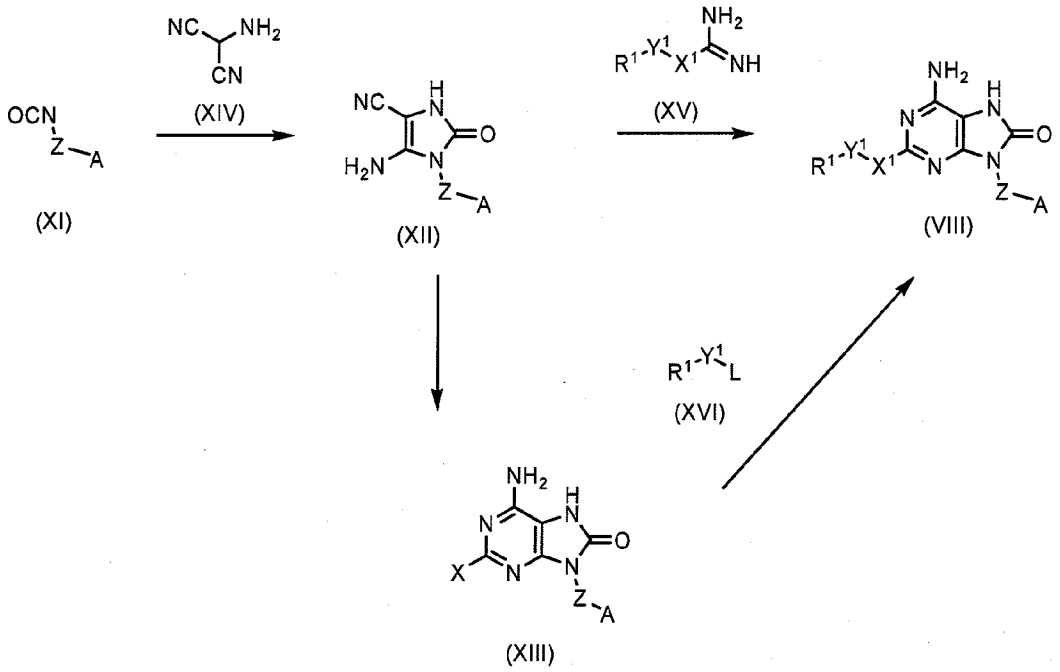
In the process of preparing the compound (VIII) from the compound (I), the compound (V) can be synthesized from the compound (II) by the same method as above or from the compound (I) through the compound (IV), and the compound (VIII) can also be obtained by converting thus-obtained compound (V) into the compound (VII).

[0045]

Preparation method 2

[0046]

[Chemical formula 9]



(wherein L is a leaving group, A, R^1, X^1, Y^1 and Z are the same as above, and X is amino group, hydroxy group or mercapto group).

The compound (XII) can be obtained by reacting the compound (XI) and the compound (XIV) in the presence of a base.

The base includes, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, a metal hydroxide such as sodium hydroxide or potassium hydroxide, an organic base such as triethylamine, diisopropyl-ethylamine, pyridine or 4-dimethylaminopyridine, or a metal alkoxide such as sodium methoxide. The solvent includes, for example, a halogenated hydrocarbon such as methylene chloride, an ether such as diethyl ether, tetrahydrofuran or 1,4-dioxane, an alcohol such as methanol or ethanol, or an aprotic solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile. The reaction temperature is selected from a range of about 0°C to around the boiling point of the solvent.

[0047]

The compound (VIII) can be prepared by reacting the compound (XII) and the compound (XV) in the presence or absence of a base.

The base includes, for example, an inorganic base such as alkali metal carbonate (e.g., sodium carbonate, potassium carbonate), an alkaline earth metal carbonate (e.g., calcium carbonate), a metal hydroxide (e.g., sodium hydroxide, potassium hydroxide), or an organic base such as a triethylamine, diisopropyl-ethylamine, pyridine or 4-dimethylaminopyridine, or a metal alkoxide such as sodium methoxide. The solvent includes, for example, an ether such as tetrahydrofuran, 1,4-dioxane or diglyme, an alcohol such as methanol or ethanol, or an aprotic solvent such as toluene, dimethylformamide or dimethyl sulfoxide. Alternatively, the reaction may be carried out without a solvent. The reaction temperature is selected from a range of room temperature to around the boiling point of the solvent.

[0048]

In the process of preparing the compound (VIII) from the compound (XII), the compound (VIII) is also obtainable after preparing the compound (XIII).

When X is amino group, the compound (XIII) can be prepared by reacting the compound (XII) and guanidine in the presence or absence of a base.

The base includes, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, a metal hydroxide such as sodium hydroxide or potassium hydroxide, an organic base such as triethylamine, diisopropyl-ethylamine, pyridine or 4-dimethylaminopyridin, or a metal alkoxide such as sodium methoxide. The solvent includes, for example, an ether such as tetrahydrofuran, 1,4-dioxane or diglyme, an alcohol such as methanol or ethanol, or an aprotic solvent such as toluene, dimethylformamide or dimethyl sulfoxide. The reaction may be carried out without a solvent. The reaction temperature is selected from a range of room temperature to around the boiling point of the

solvent.

When X is hydroxy group, the compound (XIII) can be prepared by reacting the compound (XII) and urea in the presence or absence of a base. The base includes, for example, an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, a metal hydroxide such as sodium hydroxide or potassium hydroxide, an organic base such as triethylamine, diisopropylethylamine, pyridine or 4-dimethylaminopyridine, or a metal alkoxide such as sodium methoxide. The solvent includes, for example, an ether such as tetrahydrofuran, 1,4-dioxane or diglyme, an alcohol such as methanol or ethanol, or an aprotic solvent such as toluene, dimethylformamide or dimethyl sulfoxide. The reaction may be carried out without a solvent. The reaction temperature is selected from a range of room temperature to around the boiling point of the solvent.

When X is mercapto group, the compound (XIII) can be prepared by reacting the compound (XII) and benzoyl isocyanate in the presence or absence of a base, followed by cyclization.

The base used in the reaction with benzoyl isocyanate includes an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, or an organic base such as triethylamine, diisopropylethylamine, pyridine or 4-dimethylaminopyridine. The solvent includes, for example, a halogenated hydrocarbon such as methylene chloride, an ether such as tetrahydrofuran or 1,4-dioxane, or an aprotic solvent such as dimethylformamide or dimethyl sulfoxide. The reaction temperature is selected from a range of about 0°C to around the boiling point of the solvent.

The solvent used in the cyclization reaction includes an alkali metal hydroxide such as sodium hydroxide or potassium hydroxide, a metal alkoxide such as sodium methoxide or potassium t-butoxide. The solvent includes, for example, an ether such as tetrahydrofuran, an alcohol such as ethanol or 2-propanol, or an aprotic solvent such as dimethylformamide or dimethyl sulfoxide. The reaction temperature is selected from a range of room temperature to around the boiling point of the solvent.

[0049]

The compound (VIII) can be prepared by reacting the compound (XIII) and the compound (XVI) in the presence of a base. The base includes, for example, an alkali metal hydrogen carbonate such as sodium hydrogen carbonate, an alkali metal carbonate such as sodium carbonate or potassium carbonate, an alkaline earth metal carbonate such as calcium carbonate, a metal hydroxide such as sodium hydroxide or potassium hydroxide, a metal hydride such as sodium hydride, an organic base such as triethylamine, diisopropyl-ethylamine, pyridine, or 4-dimethylaminopyridine, or a metal alkoxide such as potassium t-butoxide. The solvent includes, for example, a halogenated hydrocarbon such as carbon tetrachloride, chloroform or methylene chloride, an

ether such as diethyl ether, tetrahydrofuran or 1,4-dioxane, or an aprotic solvent such as dimethylformamide, dimethyl sulfoxide or acetonitrile. The reaction temperature is selected from a range of about 0°C to around the boiling point of the solvent.

[0050]

The compounds represented by the formulas (IX), (X), (XIV), (XV) or (XVI), which are the starting compounds of the adenine compound of the present invention, are known compounds or can be prepared by conventional methods for the skilled person in the art.

In a case where the adenine compound of the present invention or its intermediate or the starting compound therefor contains a functional group, a reaction for increasing a carbon atom, a reaction for introducing a substituent or a reaction for conversion of a functional group can be conducted optionally according to a manner conventional to the skilled artisan in an appropriate step, namely in an intermittent step in each of the preparation methods described in the preparation method 1 or 2. For this purpose, the methods described in "JIKKEN KAGAKU-KOZA (edited by NIHON KAGAKU-KAI, MARUZEN)", or "Comprehensive Organic Transformation, R. C. Lalock (VCH Publishers, Inc. 1989)" can be used. The reaction for increasing a carbon atom includes a method comprising converting an ester group to hydroxymethyl group using a reducing agent such as aluminum lithium hydride, introducing a leaving group and then introducing a cyano group. The reaction for conversion of a functional group includes a reaction for conducting acylation or sulfonylation using an acid halide, a sulfonyl halide, etc., a reaction for reacting an alkylation agent such as a halogenated alkyl, a hydrolysis reaction, a reaction for C-C bond formation such as Friedel-Crafts reaction and Wittig reaction, and oxidizing or reducing reaction, etc.

In a case where the compound of the present invention or its intermediate contains a functional group such as amino group, carboxy group, hydroxy group and oxo group, a technology of protection and de-protection can optionally be used. A preferable protecting group, a protection method and a deprotection method are described in details in "Protective Groups in Organic Synthesis 2nd Edition (John Wiley & Sons, Inc.; 1990)", etc.

[0051]

The compound (1) of the present invention and the intermediate compound for production thereof can be purified by a method known to the skilled artisan. For instance, purification can be conducted by column chromatography (e.g. silica gel column chromatography or ion exchange column chromatography) or recrystallization. As the recrystallization solvent, for instance, there can be used an alcohol such as methanol, ethanol and 2-propanol, an ether such as diethyl ether, an ester such as ethyl acetate, an aromatic hydrocarbon such as benzene and toluene, a ketone such as acetone, a

hydrocarbon such as hexane, an aprotic solvent such as dimethylformamide and acetonitrile, water and a mixture of two or more thereof. As other purification method, those described in "JIKKEN KAGAKU-KOZA (edited by NIHON KAGAKU-KAI, MARUZEN) Vol. 1", etc. can be used.

[0052]

In a case where the compound of the formula (1) of the present invention contains one or more asymmetric carbon(s), its production can be conducted by using the starting material containing those asymmetric carbon(s) or by introducing the asymmetric carbon during the production steps. For instance, an optical isomer can be obtained by using an optically active starting material or by conducting an optical resolution at a suitable stage of the production steps. The optical resolution method can be conducted by a diastereomer method comprising allowing the compound of the formula (1) or its intermediate to form a salt with an optically active acid (e.g. a monocarboxylic acid such as mandelic acid, N-benzyloxyalanine and lactic acid, a dicarboxylic acid such as tartaric acid, o-diisopropylidene tartrate and malic acid, a sulfonic acid such as camphor sulfonic acid and bromocamphor sulfonic acid) in an inert solvent (e.g. an alcohol such as methanol, ethanol, and 2-propanol, an ether such as diethyl ether, an ester such as ethyl acetate, a hydrocarbon such as toluene, an aprotic solvent such as acetonitrile and a mixture of two or more thereof).

In a case where the compound of the formula (1) or its intermediate contains an acidic functional group such as carboxylic group, it can be attained also by forming a salt with an optically active amine (e.g. an organic amine such as α-phenethylamine, quinine, quinidine, cinchonidine, cinchonine and strychnine).

[0053]

The temperature for formation of the salt is selected from a range of room temperature to the boiling point of the solvent. In order to increase optical purity, the temperature is preferably once increased up to the boiling point of the solvent. Upon recovering the precipitated salt by filtration, the yield can be increased optionally by cooling. An amount of the optical active acid or amine is about 0.5 to about 2.0 equivalent(s), preferably around 1 equivalent, to 1 equivalent of the substrate. An optically active salt with highly optical purity can be obtained optionally by recrystallization from an inert solvent (e.g. an alcohol such as methanol, ethanol and 2-propanol, an ether such as diethyl ether, an ester such as ethyl acetate, a hydrocarbon such as toluene, an aprotic solvent such as acetonitrile and a mixture of two or more thereof). If necessary, the optically resolved salt can be converted into a free form by treating with an acid or a base by the conventional method.

[0054]

The 8-oxoadenine compound of the present invention, its tautomer or its pharmaceutically acceptable salt shows an interferon inducing activity, and/or a

suppressing activity of the production of IL-4 and IL-5, and hence, they are useful as a medicament exhibiting an immunomodulating activity specific against type 1 helper T-cell (Th1 cell)/type 2 helper T-cell (Th2 cell). Namely, since they show an immunomodulating activity specific against Th2 cell, they are useful as a prophylactic or therapeutic agent for allergic diseases such as asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatosis. etc. which are caused by Th2 cell. Additionally, due to its immuno activating activity such as interferon α and interferon γ inducing activity, it is useful as a prophylactic or therapeutic agent for cancer, a viral disease caused by infection with virus such as hepatitis B virus, hepatitis C virus, HIV and human papilloma virus (HPV), infections by bacteria and dermatosis such psoriasis. In addition, the 8-oxoadenine compound of the present invention, its tautomer or its pharmaceutically acceptable salt can show the pharmacological activity at the site administered in a case of topical administration, and further they are useful as a pharmaceutical preparation for topical administration characterized by showing no systemic pharmacological activity because the compounds are converted by an enzyme in vivo into different compounds (degraded compounds) having only a substantially reduced medical effect. The medical effect used here means a pharmacological activity of the compound, including specifically an interferon inducing activity, and a suppressing activity of the production of IL-4 and/or IL-5.

The medical effect of the degraded compound is preferably 10 times, more preferably 100 times, still more preferably 1000 times reduced comparing with that of the parent compound.

[0055]

The pharmacological activity can be measured by any of conventional evaluation methods, preferably by an in vitro evaluation method. Specific examples of the methods are one described in Method in ENZYMOLOGY (Academic Press), a method using commercially available ELISA kits (e.g. AN'ALYSA (immunoassay System)) and a method described in Examples of the present specification.

For instance, by measuring interferon inducing activity with bioassay using cells of rat spleen, the amount of each interferon induction (IU/ml) at the same concentration of the parent compound (the compound of the present invention) and the degraded compound can be compared. In addition, the concentrations of the parent compound and its degraded compound at which those compounds show a prescribed interferon inducing property can be compared.

[0056]

As the pharmacological activity, the activity in vivo caused by interferon inducing activity, etc. is illustrated. Said activity in vivo includes immune activating activity, influenza-like symptom, etc. The immune activating activity

includes induction of cytotoxic activity such as natural killer (NK) cells, etc. The influenza-like symptom includes fever, etc. The fever means elevation in body temperature of a mammalian, for example, in a case of human, the fever means that the body temperature increases more than normal temperature.

[0057]

The method for topical administration is not limited, and the administration is conducted in a case of administration via nasal cavity, alveolus or air way, by aeration or inhalation, in a case of administration to skin, by spreading on the skins, and in a case of administration to eye, by eye dropping, etc. Preferable administration is aeration and inhalation.

[0058]

It can be confirmed by its half life in the serum or in liver S9 in the in vitro evaluation test that when the composition of the present invention is administered topically, the compound of the present invention is degraded in the blood in human or animal and converted into a degraded compound. The test method to determine the half life of the compound of the present invention in the in vitro evaluation test is known.

In the in vitro evaluation test, the compound of the present invention is metabolized in liver S9 and its half life is preferably not longer than 60 minutes, more preferably not longer than 30 minutes, and still more preferably not longer than 10 minutes. Further, the compound of the present invention is metabolized in serum, and its half life is preferably not longer than 60 minutes, more preferably not longer than 30 minutes, and still more preferably not longer than 10 minutes.

[0059]

The above-mentioned "degraded compound" is a compound having a carboxy group or phosphonic group obtained by hydrolyzing an ester group in the formula (1).

[0060]

The method for measuring the half life in liver S9 of the present invention is as follows. Namely, the compound of the present invention is added to a liver S9 solution and incubated at 37±0.5°C for 5 minutes to 2 hours. By quantitatively analyzing at regular time intervals the amount of the compound of the present invention remaining in the liver S9 solution with HPLC (high performance liquid chromatograph), etc., the elimination rate constant is obtained and the half life is calculated therefrom. The specific method is described in Example.

The liver S9 used herein means a product obtained by homogenizing a liver of a mammal in an aqueous solution such as a physiological saline solution, a sucrose solution and a KCl solution and then by recovering the supernatant upon centrifugation at 9000 xg. The aqueous solution is used usually in an amount of 2 to 4 times as much as the liver. The mammal includes human, dog,

rabbit, guinea pig, mouse and rat. The liver S9 can be used optionally after diluting with a buffering solution.

[0061]

The measuring method for the half life in serum of the compound of the present invention is as follows. Namely, the compound of the present invention is added to a serum solution and incubated at 37±0.5°C for 5 minutes to 2 hours. By quantitatively analyzing at regular time intervals the amount of the compound of the present invention remaining in the serum solution with HPLC (high performance liquid chromatograph), etc., the elimination rate constant is obtained and the half life is calculated therefrom.

The serum used here means a supernatant fraction obtained by removing hemocytes and blood coagulation factors from the blood by centrifugation, etc. and it may be used after diluting with a buffering solution.

[0062]

The compound of the present invention has no limitation as to its pharmaceutical formulation as long as it can be administered topically. The pharmaceutical formulation is prepared by a conventional method, and it can contain a conventional carrier, excipient, binder, stabilizer, buffering agent, solubilizer, isotonic agent, etc.

The preparation for topical administration can be exemplified by ointments, lotions, creams, gels, tapes, transdermal patches, cataplasms, sprays, aerosols, liquids/suspensions for cartridge spray for inhalators or insufflators, ear drops, nasal drops, powders for external application, and the like.

The ointments, creams and gels contain the compound of the present invention usually in an amount of 0.01-10 w/w %, and there may be incorporated a thickener and/or a gelling agent and/or a solvent, which are suitable to an aqueous or oily base. The base is exemplified by water and/or an oil such as liquid paraffin, a vegetable oil such as arachis oil and castor oil, a solvent such as polyethylene glycol, and so on. The thickener and the gelling agent are exemplified by soft paraffin, aluminum stearate, cetostearic alcohol, polyethylene glycol, sheep fat, beeswax, carboxypolymethylene and cellulose derivatives and/or glyceryl monostearate and/or nonionic emulsifiers.

The lotions contain the compound of the present invention usually in an amount of 0.01-10 w/w %, and it may be prepared with the use of an aqueous or oily base, and it may generally contain emulsifiers, stabilizers, dispersing agents, precipitation inhibitors and also thickeners.

The powders for external use contain the compound of the present invention usually an amount of 0.01-10 w/w %, and it may be formulated using a suitable powdery base such as talc, lactose and starch.

The drips may be formulated by using an aqueous or non-aqueous base, and may contain dispersing agents, solubilizing agents, precipitation inhibitors or antiseptics.

The sprays may be formulated into an aqueous solution or suspension using a suitable liquid propellant, or into an aerosol distributed from a pressured package such as a metered-dose inhaler.

The aerosols suitable to inhalation may be either a suspension or solution, and they generally contain the compound of the present invention and a suitable propellant such as fluorocarbon, hydrogen-containing chlorofluorocarbon or a mixture thereof, particularly hydrofluoroalkane, specifically 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. The aerosols may optionally contain additional excipients well known in the art such as a surfactant, (e.g., oleic acid or lecithin) and a co-solvent such as ethanol.

The gelatin capsules or cartridges used for inhalator or insufflator may be formulated by using a powdery mixture of the compounds used in the present invention and a suitable powdery base such as lactose and starch. Each capsule or cartridge usually contains the compound of the present invention in an amount of 20 μg-10 mg. Alternatively, the compound of the present invention may be administered without using excipients such as lactose.

The ratio of the active compound of the present invention in the preparation for topical administration of the present invention is, though depending upon the formulation, generally 0.001-10 wt %, preferably 0.005-1%. The ratio used in the powders for inhalation or insufflation is in the range of 0.1-5 %.

In a case of aerosols, the compound of the present invention is preferably contained in an amount of 20 μg -2000 μg, more preferably about 20 μg-500 μg per each a measured amount or one sprayed amount. The dosage is once or several times per day, for instance, 2, 3, 4 or 8 times per day, and one to three dosage units are administered per each time.

[0063]

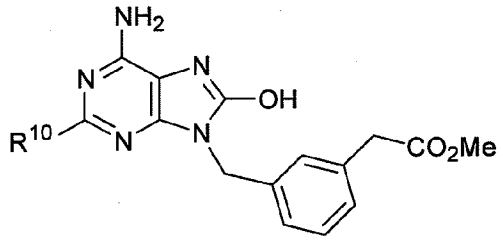
The pharmaceutical composition of the present invention may be used together with another therapeutically effective medicament. For example, when it is used as an antiasthmatic drug, it can be used together with beta 2-adrenoceptor agonist, antihistamine or antiallergic, especially beta 2-adrenoceptor agonist. Each compound used in this combination may be administered either succesively or simultaneously in a discrete form or in the form of a combination thereof.

[0064]

The compounds of the present invention are illustrated in the following Tables 2 to 45, but should not be limited to these compounds. In the following Tables 2 to 45, the chemical structures of the compounds of the present invention are expressed in a form of 8-hydroxy type for convenience, but those are not intended to be different from the form of 8-oxo type.

[0065]

[Table 2]



$-R^{10}$
$-O(CH_2)_5OH$
$-O(CH_2)_2OPr$
$-O(CH_2)_3OMe$
$-O(CH_2)_3OEt$
$-O(CH_2)_4OMe$
$-O(CH_2)_2SMe$
$-O(CH_2)_2SEt$
$-O(CH_2)_3SMe$
$-O(CH_2)_2SO_2Me$
$-O(CH_2)_2SO_2Et$
$-O(CH_2)_3SO_2Me$

$-R^{10}$
$-O(CH_2)_2NMe_2$
$-O(CH_2)_3NMe_2$
$-O(CH_2)_2CF_2CF_3$
$-S(CH_2)_3OMe$
$-S(CH_2)_2SMe$
$-S(CH_2)_3SMe$
$-S(CH_2)_3Me$
$-S(CH_2)_3CF_3$
$-NH(CH_2)_2OH$
$-NH(CH_2)_3OH$
$-NH(CH_2)_4OH$

$-R^{10}$
$-NH(CH_2)_3OMe$
$-NH(CH_2)_2SMe$
$-NH(CH_2)_3SMe$
$-NH(CH_2)_3CF_3$
$-NMe(CH_2)_3OMe$
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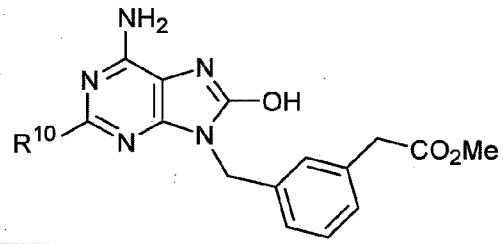
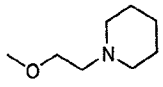
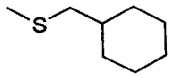
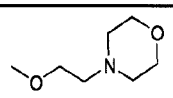
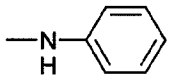
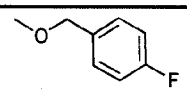
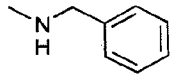
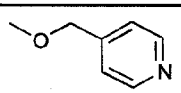
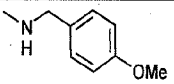
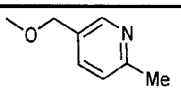
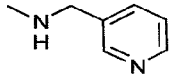
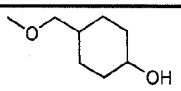
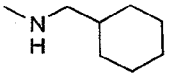
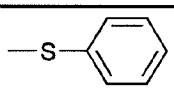
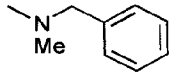
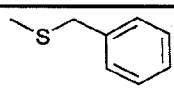
$-CH_2COOMe$
$-CF_3$

[0066]

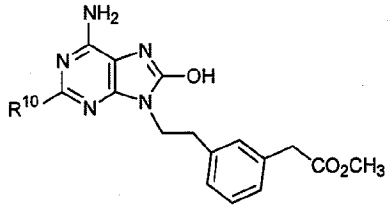
[Table 3]



$-R^{10}$	$-R^{10}$
	
	
	
	
	
	
	
	

[0067]

[Table 4]



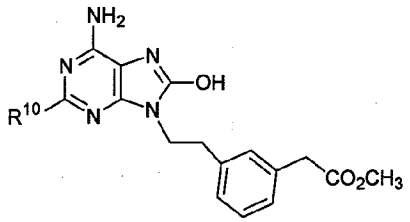
$-R^{10}$
$-O(CH_2)_2OH$
$-O(CH_2)_3OH$
$-O(CH_2)_4OH$
$-O(CH_2)_5OH$
$-O(CH_2)_2OMe$
$-O(CH_2)_2OEt$
$-O(CH_2)_2OPr$
$-O(CH_2)_3OMe$
$-O(CH_2)_3OEt$
$-O(CH_2)_4OMe$
$-O(CH_2)_2SMe$
$-O(CH_2)_2SEt$
$-O(CH_2)_3SMe$
$-O(CH_2)_2SO_2Me$

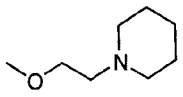
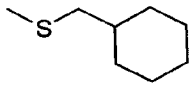
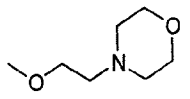
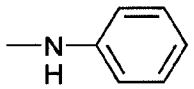
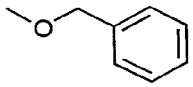
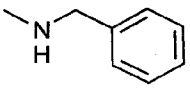
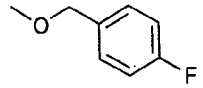
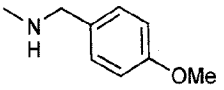
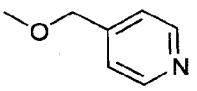
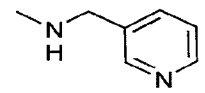
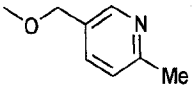
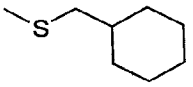
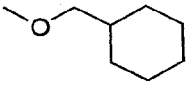
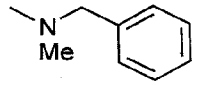
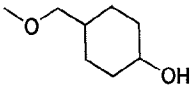
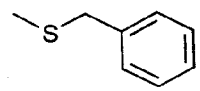
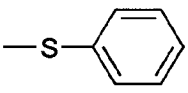
$-R^{10}$
$-O(CH_2)_2SO_2Et$
$-O(CH_2)_3SO_2Me$
$-O(CH_2)_2NMe_2$
$-O(CH_2)_3NMe_2$
$-O(CH_2)_3CF_3$
$-O(CH_2)_2CF_2CF_3$
$-S(CH_2)_2OH$
$-S(CH_2)_3OH$
$-S(CH_2)_4OH$
$-S(CH_2)_2OMe$
$-S(CH_2)_3OMe$
$-S(CH_2)_2SMe$
$-S(CH_2)_3SMe$
$-S(CH_2)_3Me$

$-R^{10}$
$-S(CH_2)_3CF_3$
$-NH(CH_2)_2OH$
$-NH(CH_2)_3OH$
$-NH(CH_2)_4OH$
$-N(CH_2)_2OMe$
$-NH(CH_2)_3OMe$
$-NH(CH_2)_2SMe$
$-NH(CH_2)_3SMe$
$-NH(CH_2)_3Me$
$-NH(CH_2)_3CF_3$
$-NMe(CH_2)_3OMe$
$-NMe(CH_2)_3CH_3$
$-CH_2COOMe$
$-(CH_2)_2COOMe$
$-CF_3$

[0068]

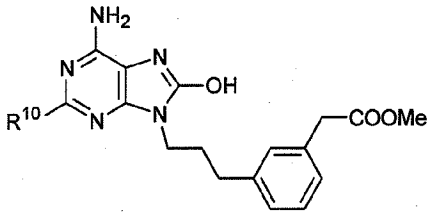
[Table 5]



$-R^{10}$	$-R^{10}$
	
	
	
	
	
	
	
	
	

[0069]

[Table 6]



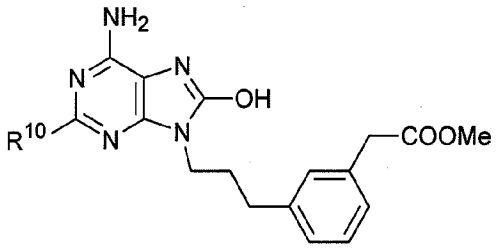
$-R^{10}$
$-O(CH_2)_2OH$
$-O(CH_2)_3OH$
$-O(CH_2)_4OH$
$-O(CH_2)_5OH$
$-O(CH_2)_2OMe$
$-O(CH_2)_2OEt$
$-O(CH_2)_2OPr$
$-O(CH_2)_3OMe$
$-O(CH_2)_3OEt$
$-O(CH_2)_4OMe$
$-O(CH_2)_2SMe$
$-O(CH_2)_2SEt$
$-O(CH_2)_3SMe$
$-O(CH_2)_2SO_2Me$

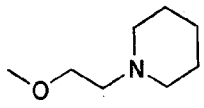
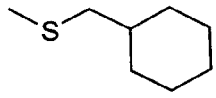
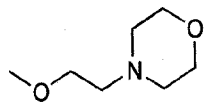
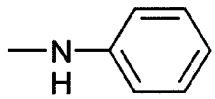
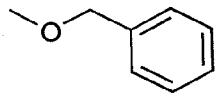
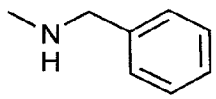
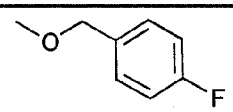
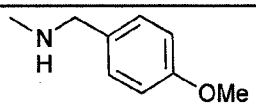
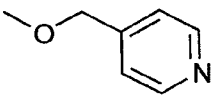
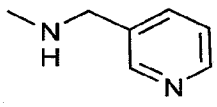
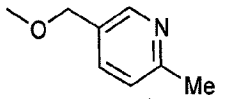
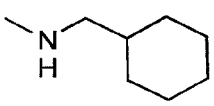
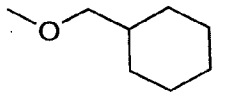
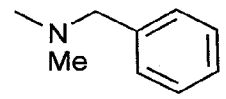
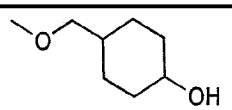
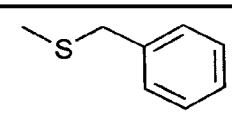
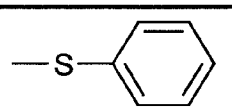
$-R^{10}$
$-O(CH_2)_2SO_2Et$
$-O(CH_2)_3SO_2Me$
$-O(CH_2)_2NMe_2$
$-O(CH_2)_3NMe_2$
$-O(CH_2)_3CF_3$
$-O(CH_2)_2CF_2CF_3$
$-S(CH_2)_2OH$
$-S(CH_2)_3OH$
$-S(CH_2)_4OH$
$-S(CH_2)_2OMe$
$-S(CH_2)_3OMe$
$-S(CH_2)_2SMe$
$-S(CH_2)_3SMe$
$-S(CH_2)_3Me$

$-R^{10}$
$-S(CH_2)_3CF_3$
$-NH(CH_2)_2OH$
$-NH(CH_2)_3OH$
$-NH(CH_2)_4OH$
$-N(CH_2)_2OMe$
$-NH(CH_2)_3OMe$
$-NH(CH_2)_2SMe$
$-NH(CH_2)_3SMe$
$-NH(CH_2)_3Me$
$-NH(CH_2)_3CF_3$
$-NMe(CH_2)_3OMe$
$-NMe(CH_2)_3CH_3$
$-CH_2COOMe$
$-(CH_2)_2COOMe$
$-CF_3$

[0070]

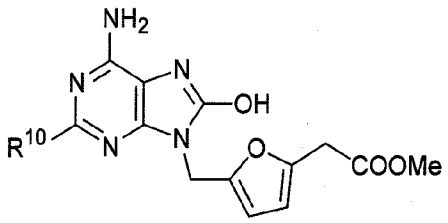
[Table 7]



$-R^{10}$	$-R^{10}$
	
	
	
	
	
	
	
	
	

[0071]

[Table 8]



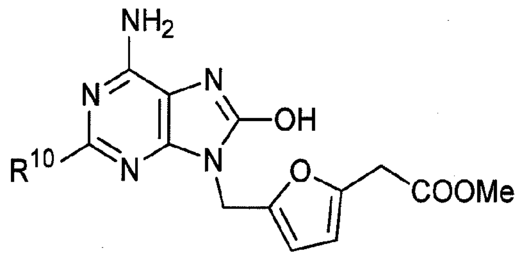
$-R^{10}$
$-O(CH_2)_2OH$
$-O(CH_2)_3OH$
$-O(CH_2)_4OH$
$-O(CH_2)_5OH$
$-O(CH_2)_2OMe$
$-O(CH_2)_2OEt$
$-O(CH_2)_2OPr$
$-O(CH_2)_3OMe$
$-O(CH_2)_3OEt$
$-O(CH_2)_4OMe$
$-O(CH_2)_2SMe$
$-O(CH_2)_2SEt$
$-O(CH_2)_3SMe$
$-O(CH_2)_2SO_2Me$

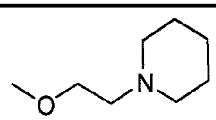
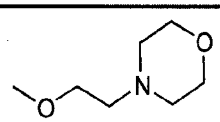
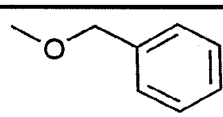
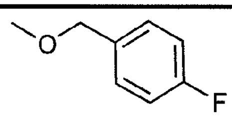
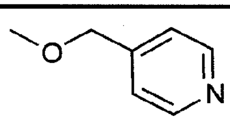
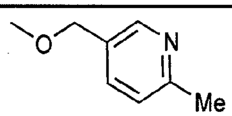
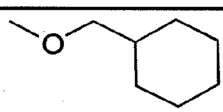
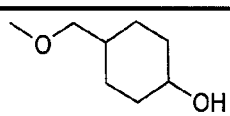
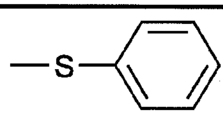
$-R^{10}$
$-O(CH_2)_2SO_2Et$
$-O(CH_2)_3SO_2Me$
$-O(CH_2)_2NMe_2$
$-O(CH_2)_3NMe_2$
$-O(CH_2)_3CF_3$
$-O(CH_2)_2CF_2CF_3$
$-S(CH_2)_2OH$
$-S(CH_2)_3OH$
$-S(CH_2)_4OH$
$-S(CH_2)_2OMe$
$-S(CH_2)_3OMe$
$-S(CH_2)_2SMe$
$-S(CH_2)_3SMe$
$-S(CH_2)_3Me$

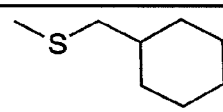
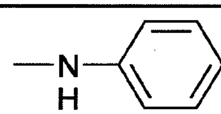
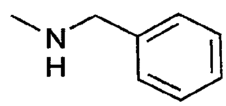
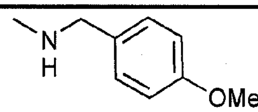
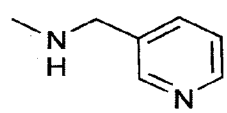
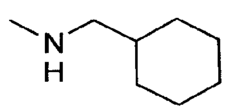
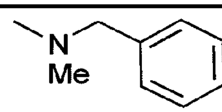
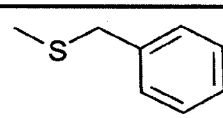
$-R^{10}$
$-S(CH_2)_3CF_3$
$-NH(CH_2)_2OH$
$-NH(CH_2)_3OH$
$-NH(CH_2)_4OH$
$-N(CH_2)_2OMe$
$-NH(CH_2)_3OMe$
$-NH(CH_2)_2SMe$
$-NH(CH_2)_3SMe$
$-NH(CH_2)_3Me$
$-NH(CH_2)_3CF_3$
$-NMe(CH_2)_3OMe$
$-NMe(CH_2)_3CH_3$
$-CH_2COOMe$
$-(CH_2)_2COOMe$
$-CF_3$

[0072]

[Table 9]

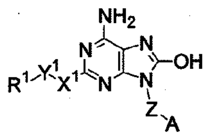


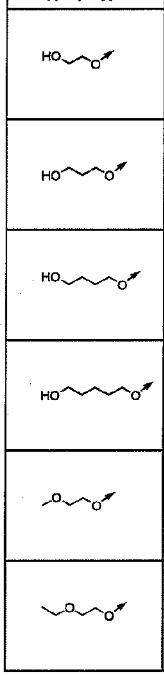
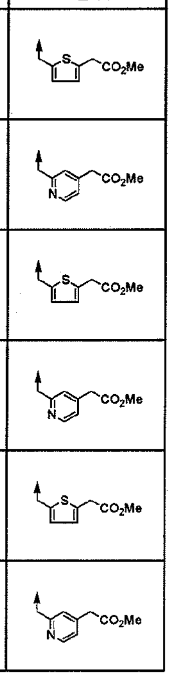
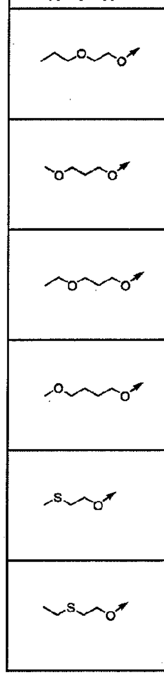
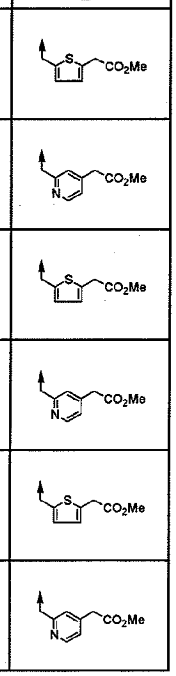
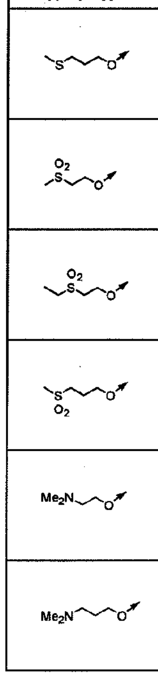
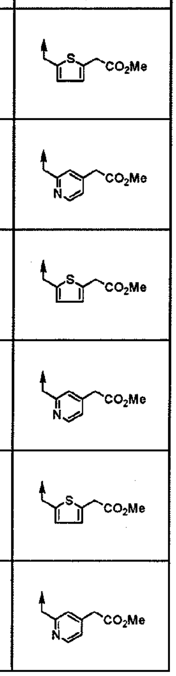
$-R^{10}$










$-R^{10}$









[0073]

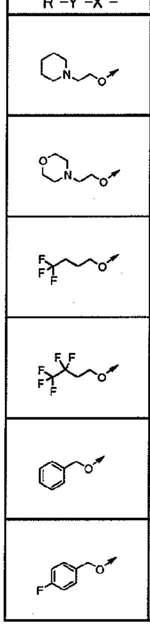
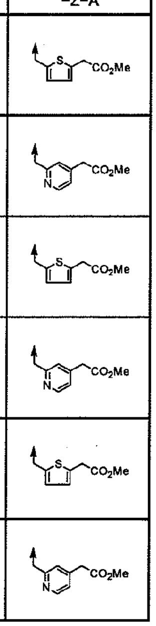
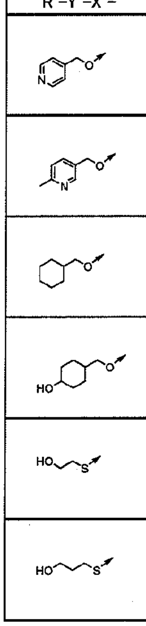
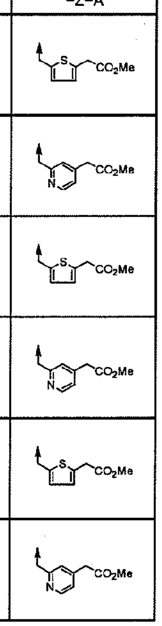
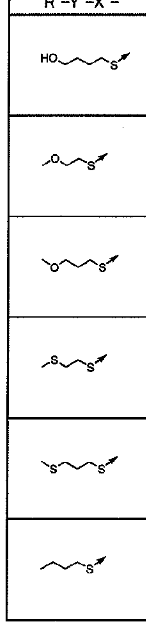
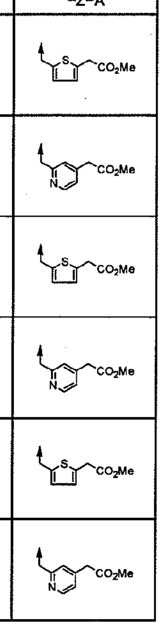
[Table 10]



R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

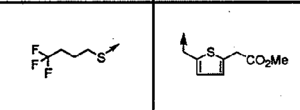
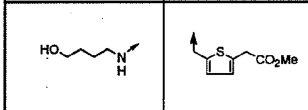
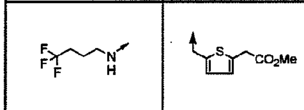
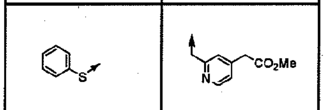
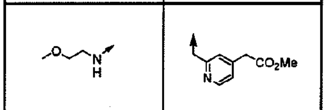
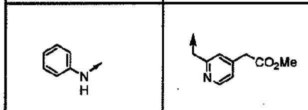
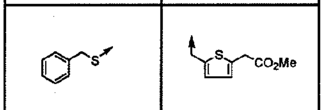
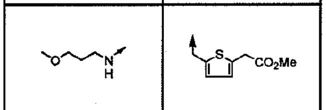
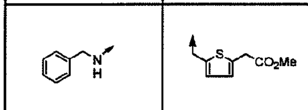
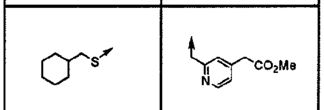
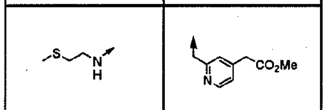
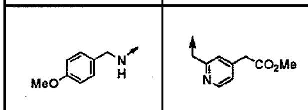
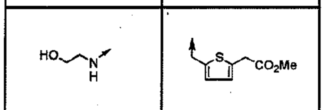
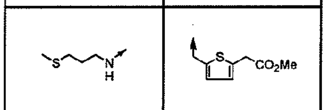
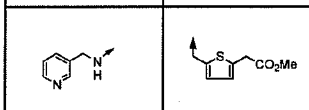
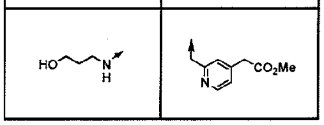
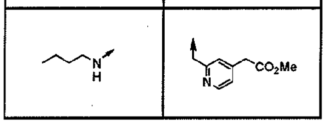
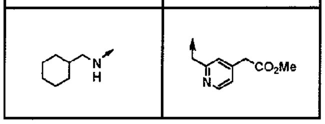
[0074]

[Table 11]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

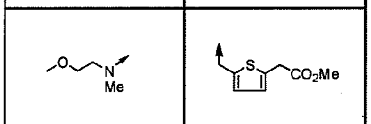
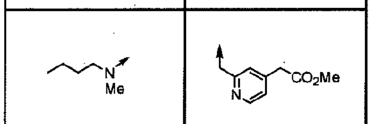
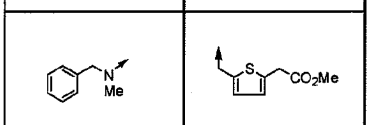
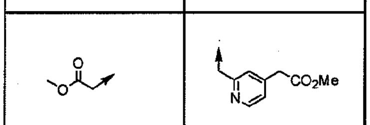
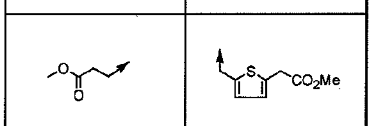
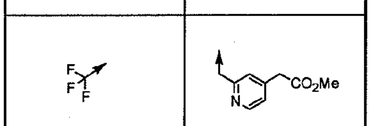
[0075]

[Table 12]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					
					
					
					
					
					

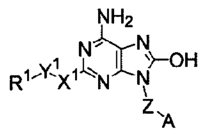
[0076]

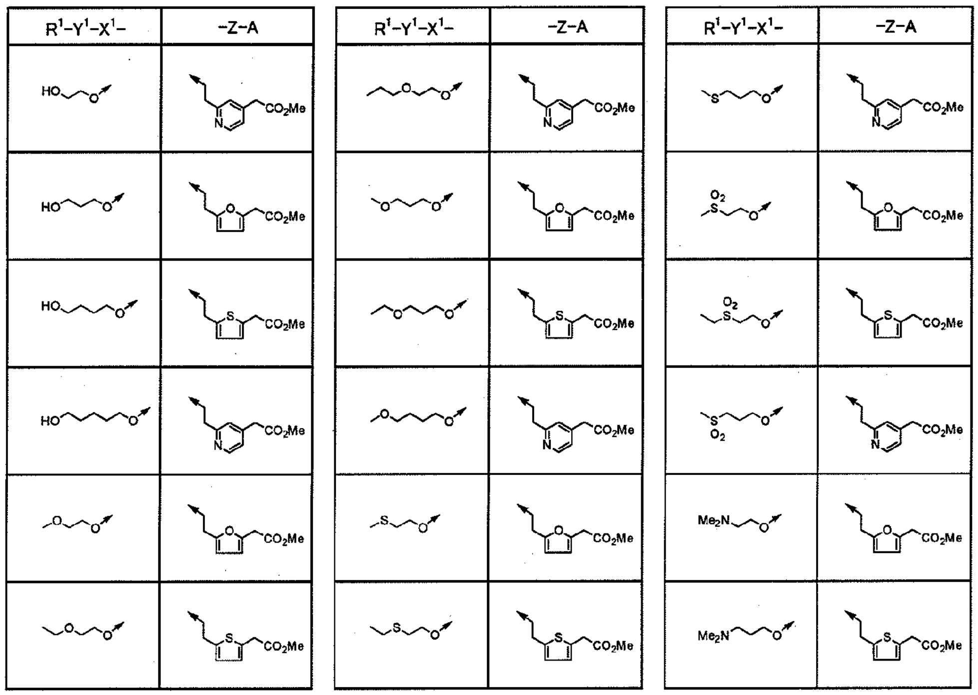
[Table 13]

R^1-Y^1-X^1-	-Z-A
	
	
	
	
	
	

[0077]

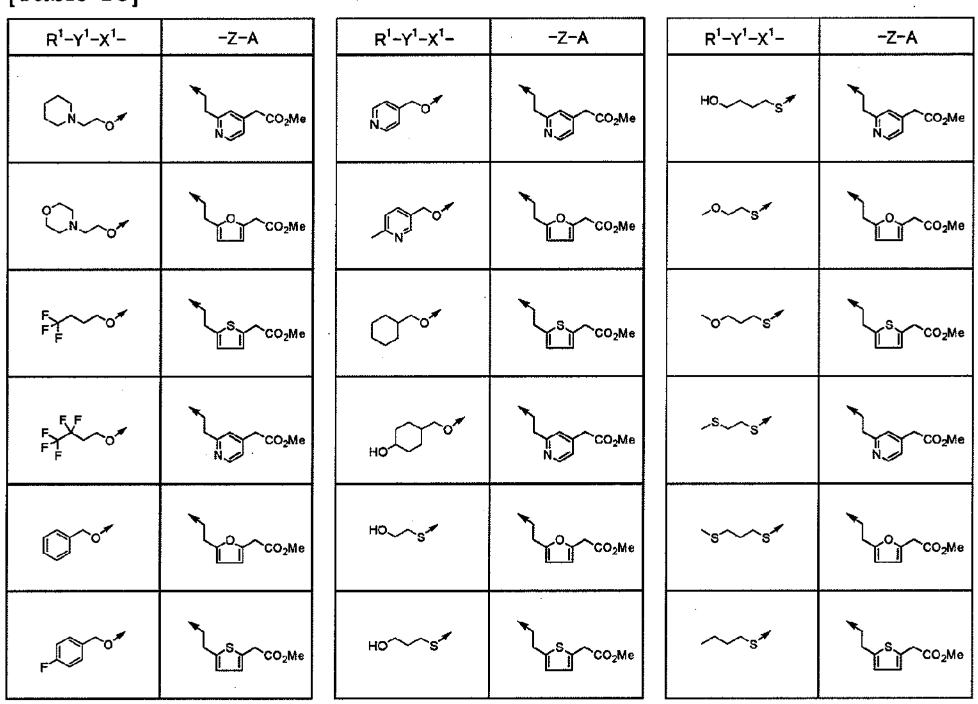
[Table 14]





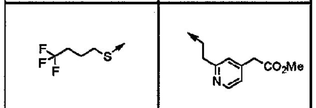
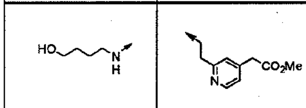
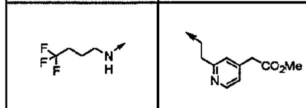
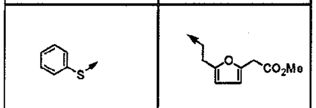
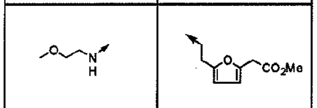
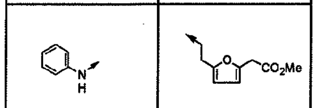
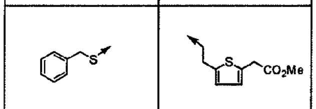
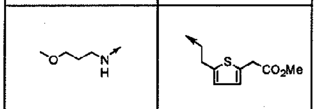
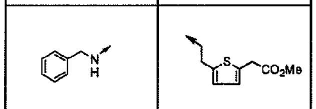
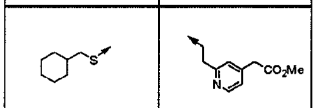
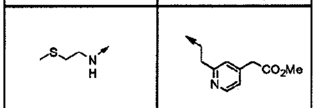
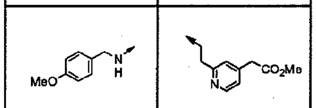
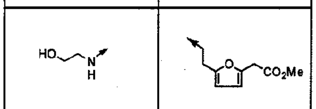
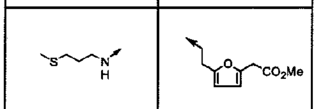
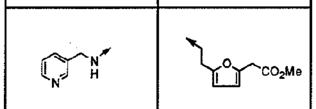
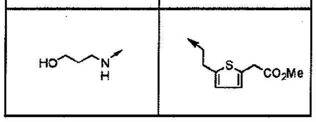
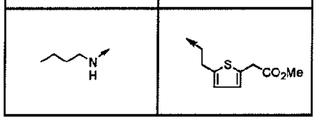
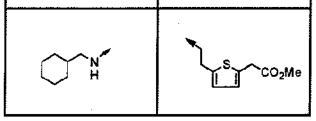
[0078]

[Table 15]



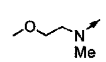
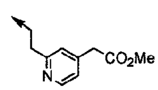
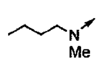
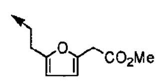
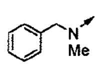
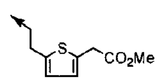
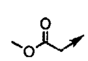
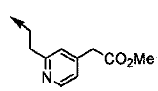
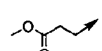
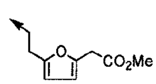
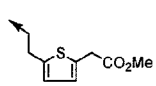
[0079]

[Table 16]

R^1-Y^1-X^1- / -Z-A	R^1-Y^1-X^1- / -Z-A	R^1-Y^1-X^1- / -Z-A
		
		
		
		
		
		

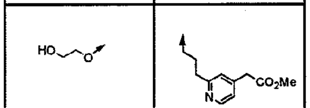
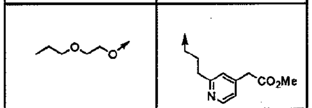
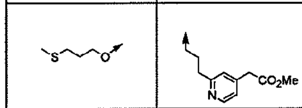
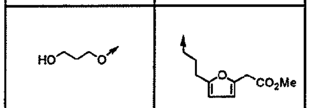
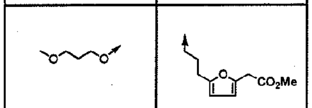
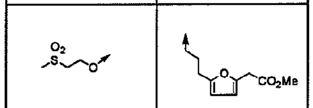
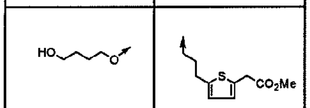
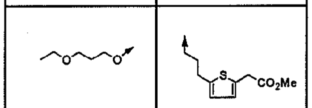
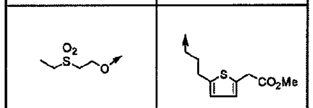
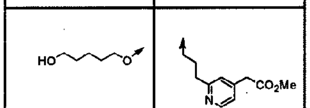
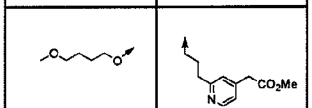
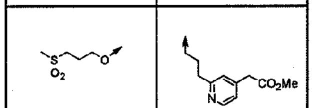
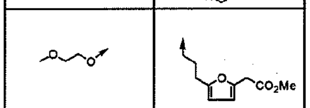
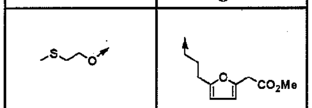
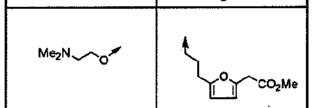
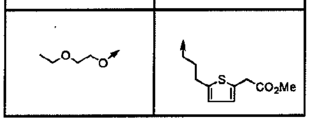
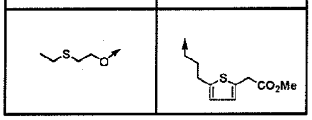
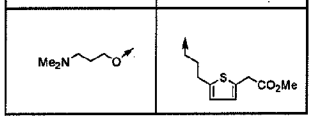
[0080]

[Table 17]

R^1-Y^1-X^1-	-Z-A
	
	
	
	
	
	

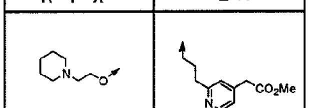
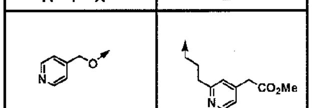
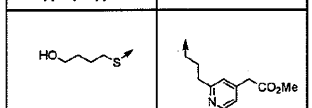
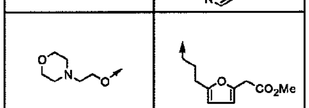
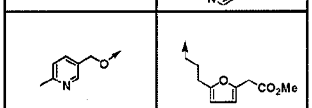
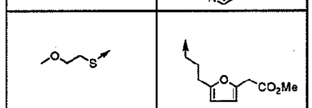
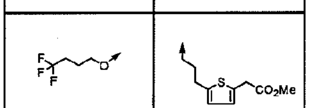
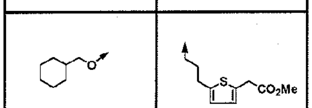
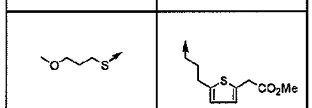
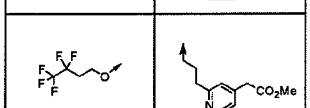
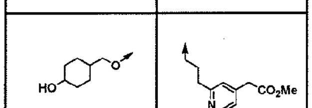
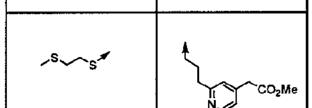
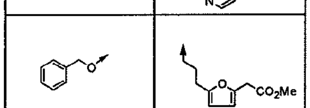
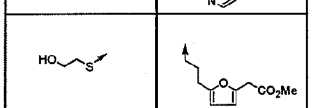
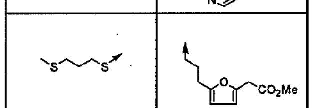
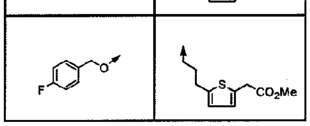
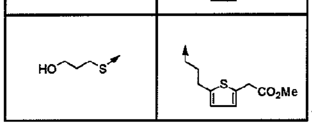
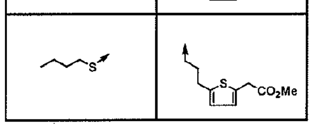
[0081]

[Table 18]

R^1-Y^1-X^1- / -Z-A	R^1-Y^1-X^1- / -Z-A	R^1-Y^1-X^1- / -Z-A
		
		
		
		
		
		

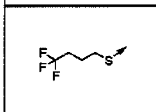
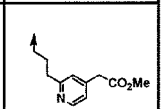
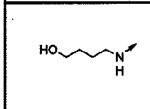
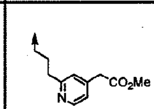
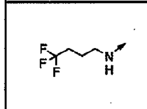
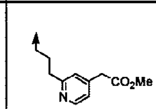
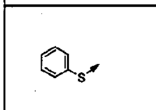
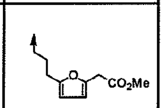
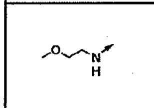
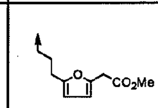
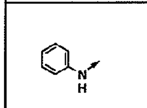
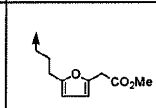
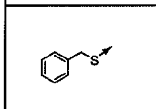
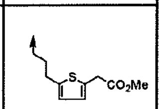
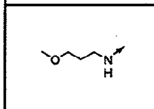
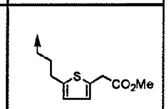
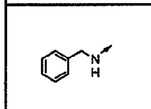
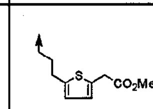
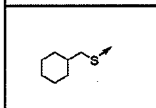
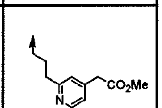
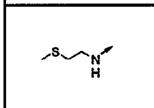
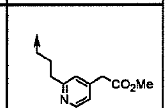
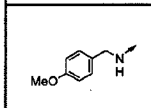
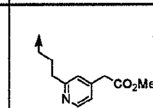
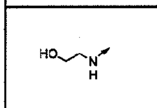
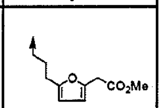
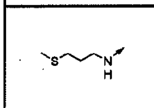
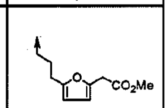
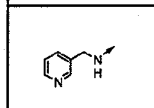
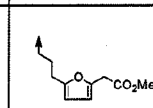
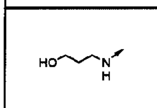
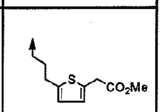
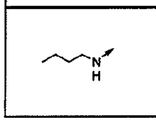
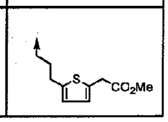
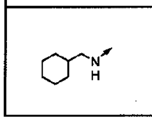
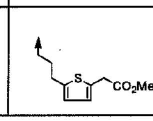
[0082]

[Table 19]

R^1-Y^1-X^1- / -Z-A	R^1-Y^1-X^1- / -Z-A	R^1-Y^1-X^1- / -Z-A
		
		
		
		
		
		

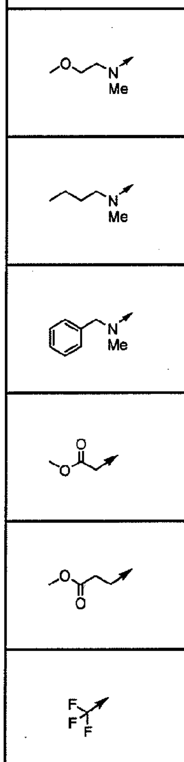
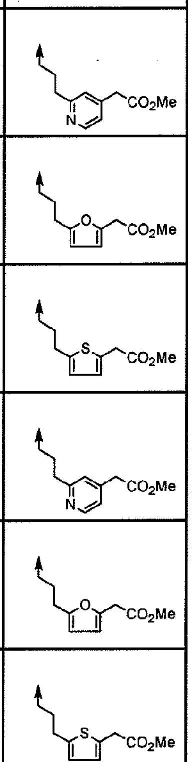
[0083]

[Table 20]

R¹-Y¹-X¹-	-Z-A	R¹-Y¹-X¹-	-Z-A	R¹-Y¹-X¹-	-Z-A
					
					
					
					
					
					

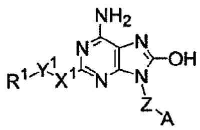
[0084]

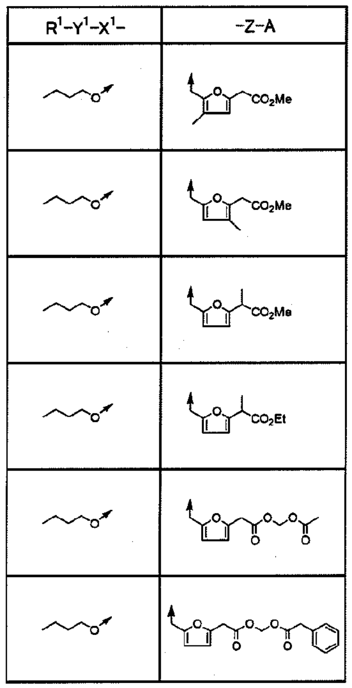
[Table 21]

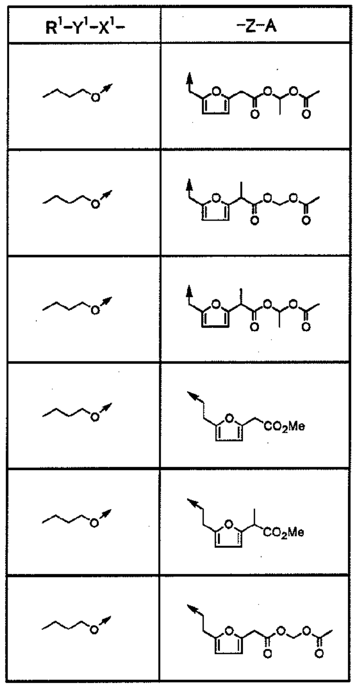
R¹-Y¹-X¹-	-Z-A
	

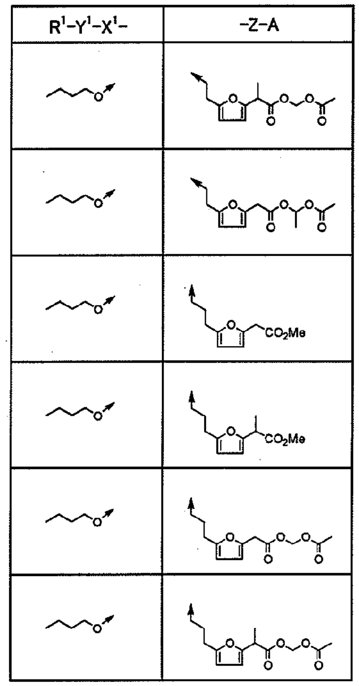
[0085]

[Table 22]



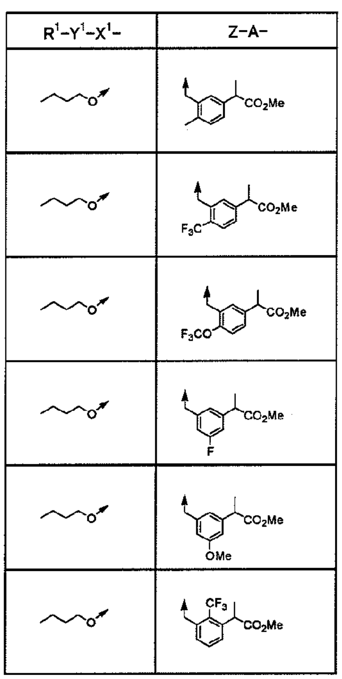


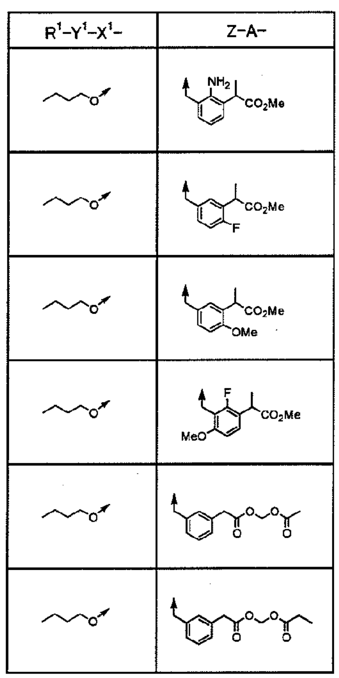


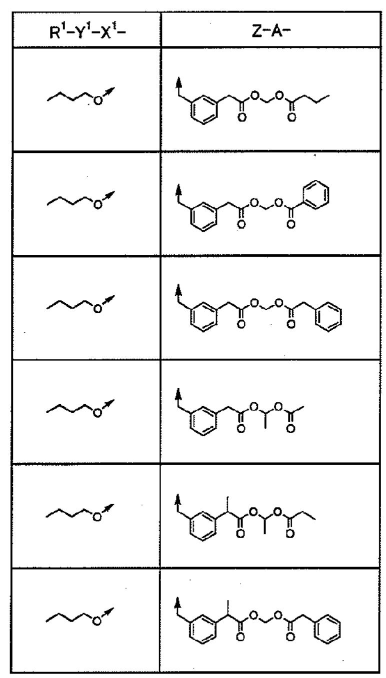


[0086]

[Table 23]

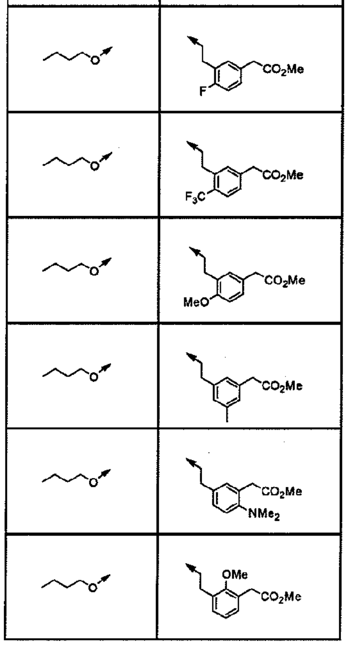
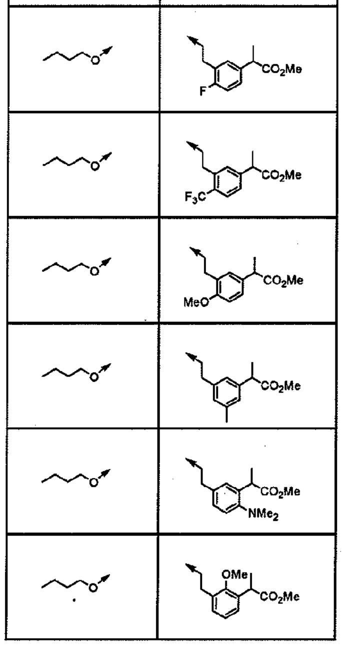
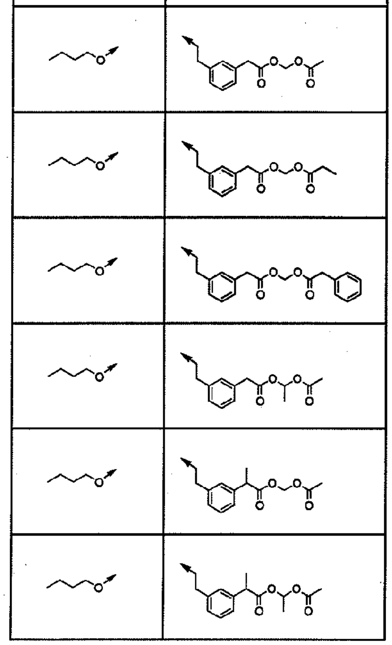






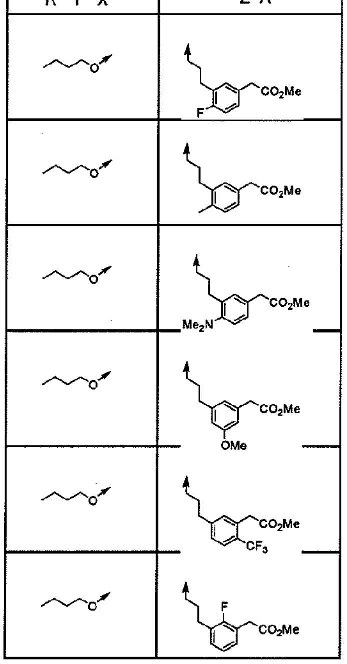
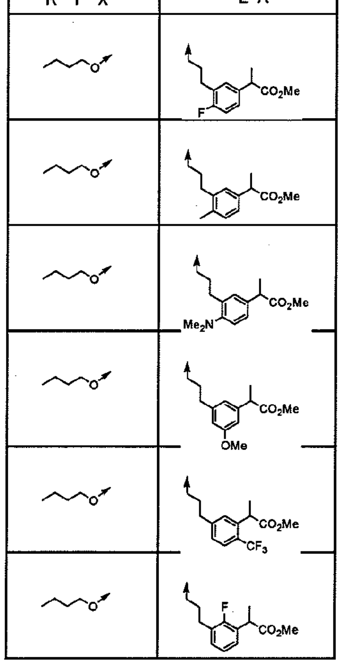
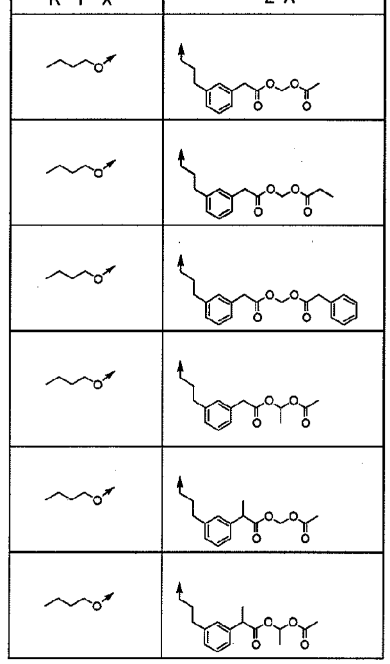
[0087]

[Table 24]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

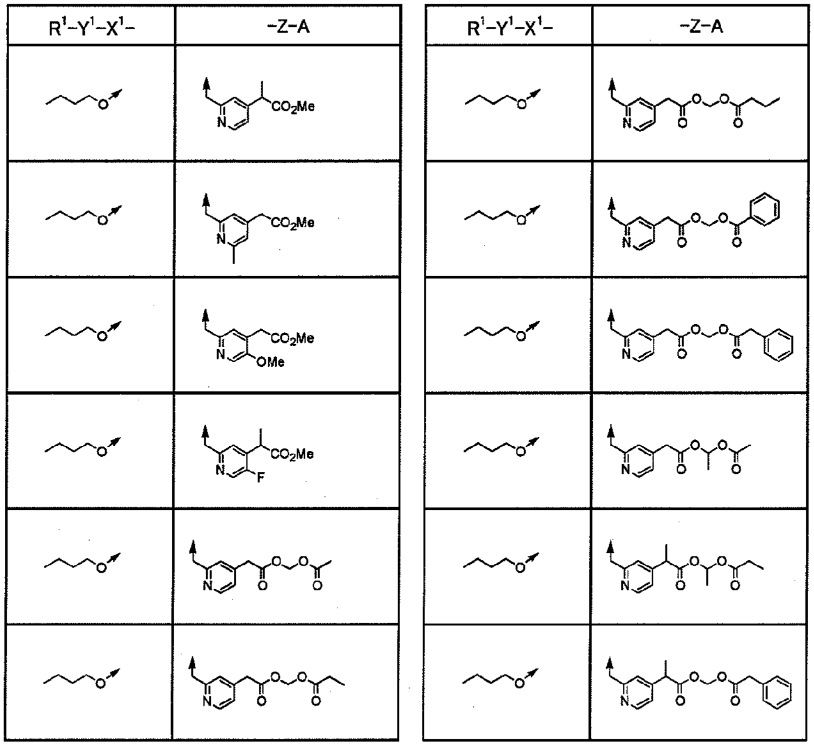
[0088]

[Table 25]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

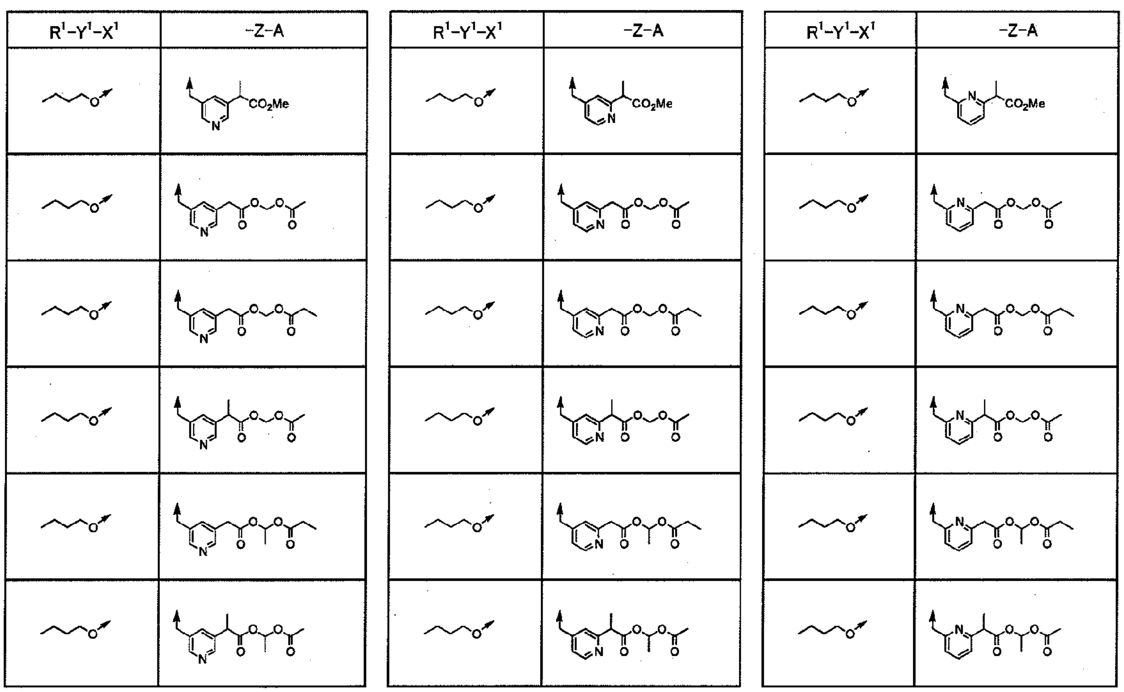
[0089]

[Table 26]



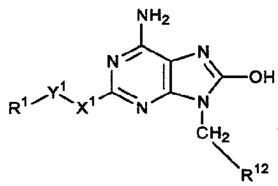
[0090]

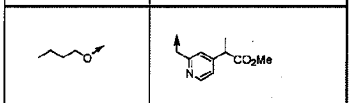
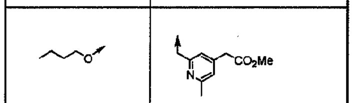
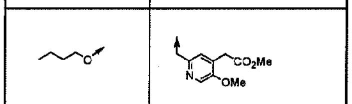
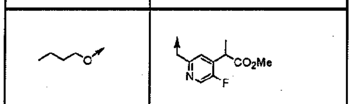
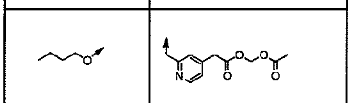
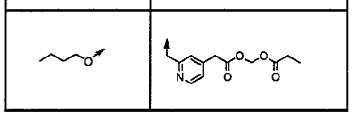
[Table 27]

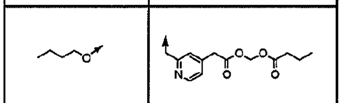
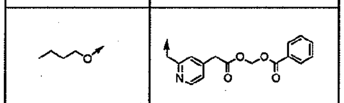
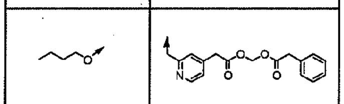
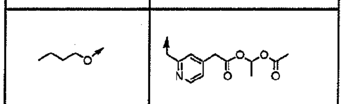
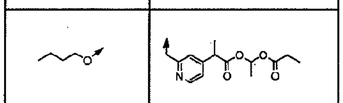
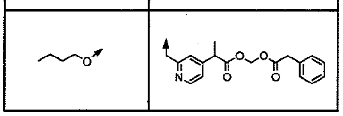


[0091]

[Table 28]

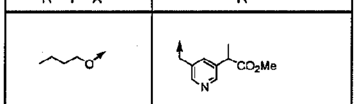
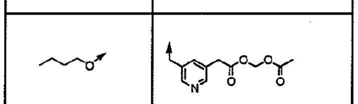
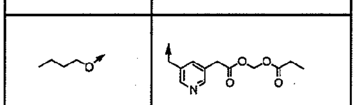
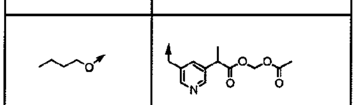
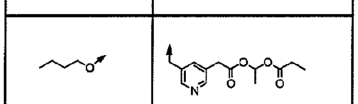
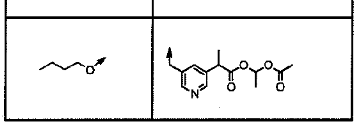


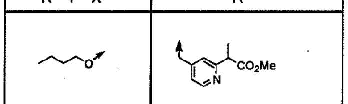
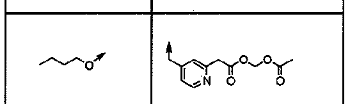
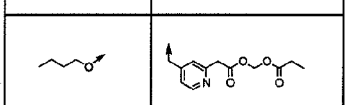
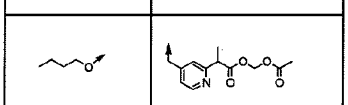
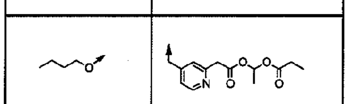
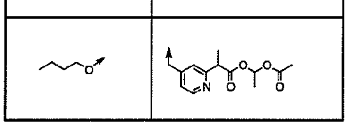
R^1-Y^1-X^1-	R^{12}-
	
	
	
	
	
	

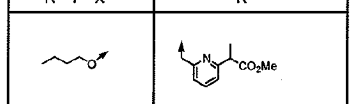
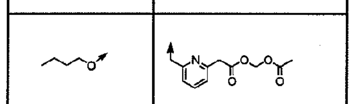
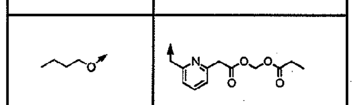
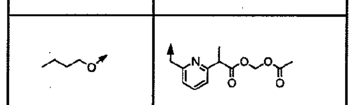
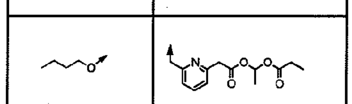
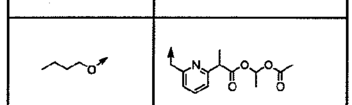
R^1-Y^1-X^1-	R^{12}-
	
	
	
	
	
	

[0092]

[Table 29]

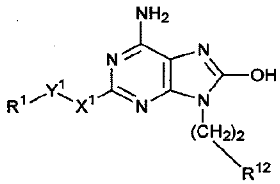
R^1-Y^1-X^1-	R^{12}-
	
	
	
	
	
	

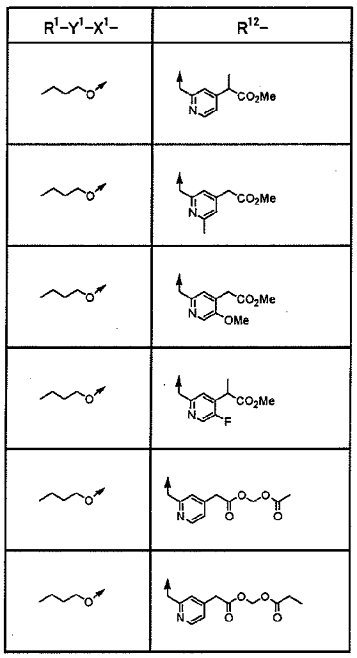
R^1-Y^1-X^1-	R^{12}-
	
	
	
	
	
	

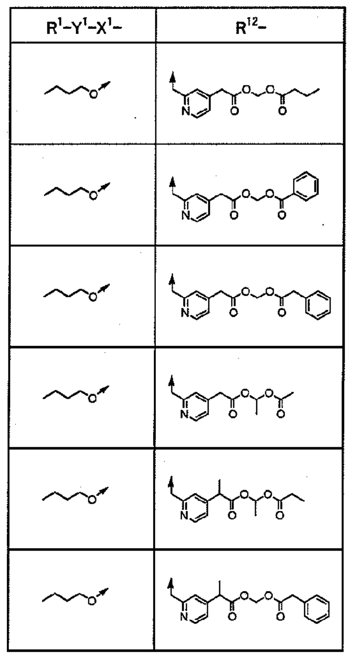
R^1-Y^1-X^1-	R^{12}-
	
	
	
	
	
	

[0093]

[Table 30]

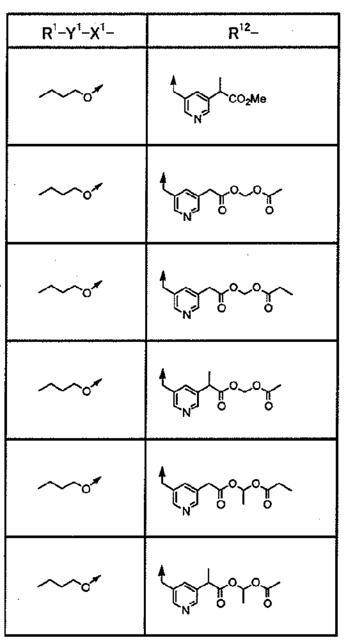


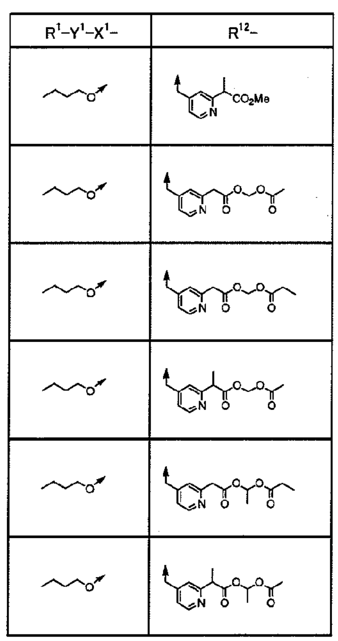


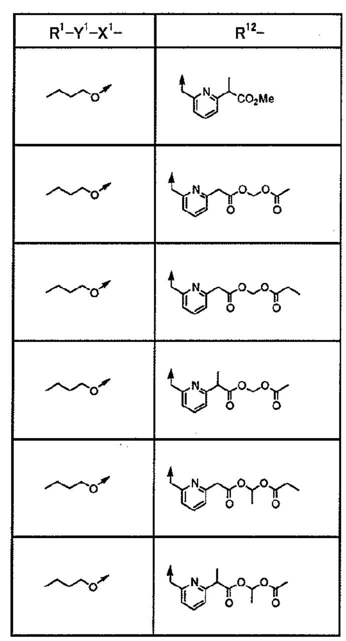


[0094]

[Table 31]

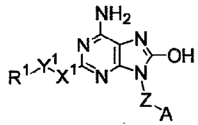


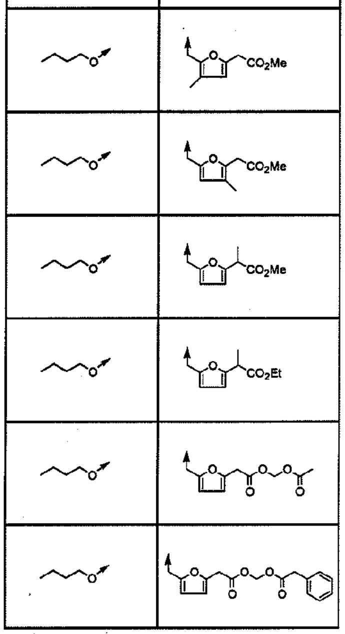
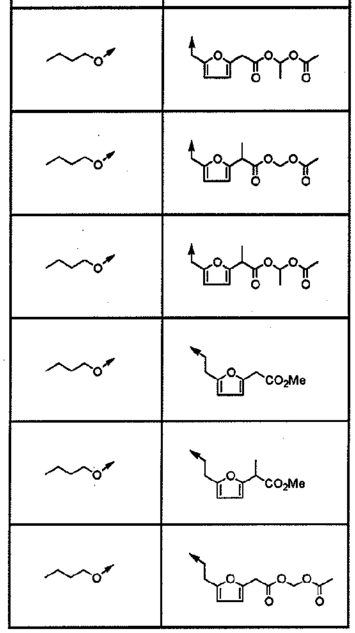
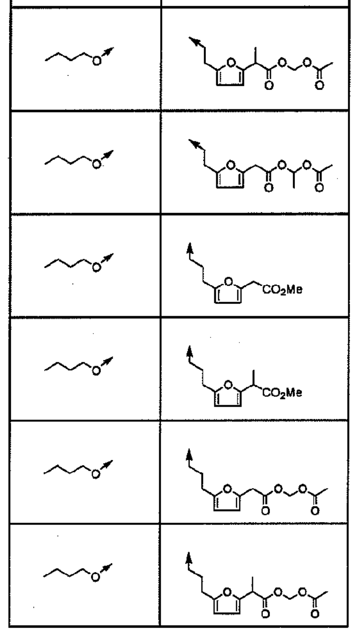




[0095]

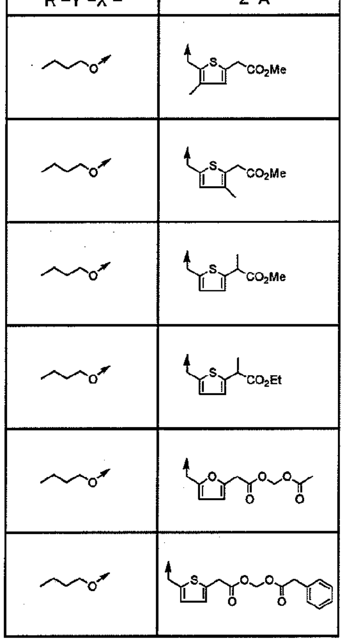
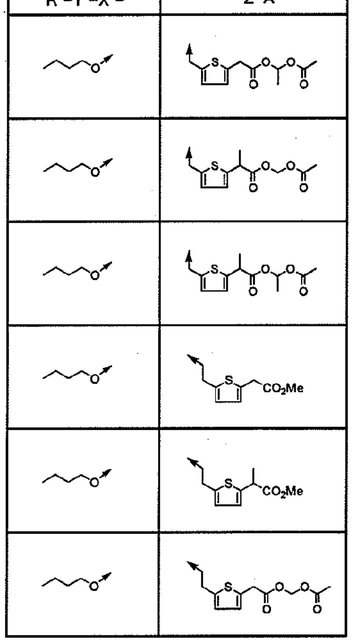
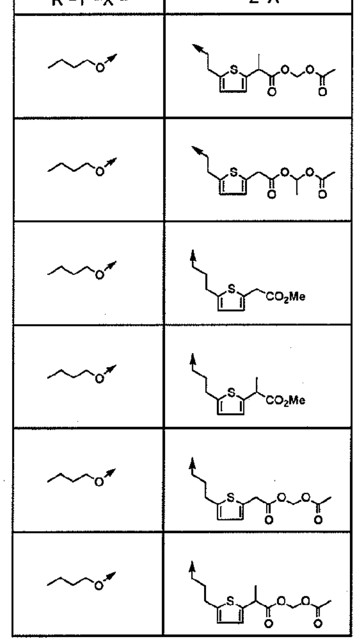
[Table 32]



R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

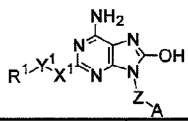
[0096]

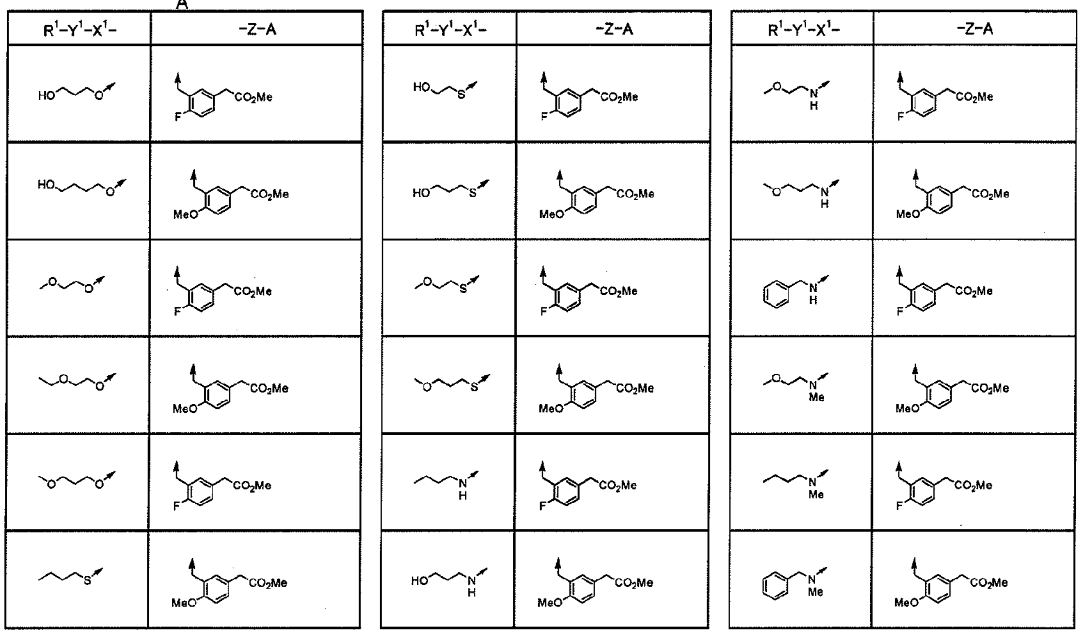
[Table 33]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

[0097]

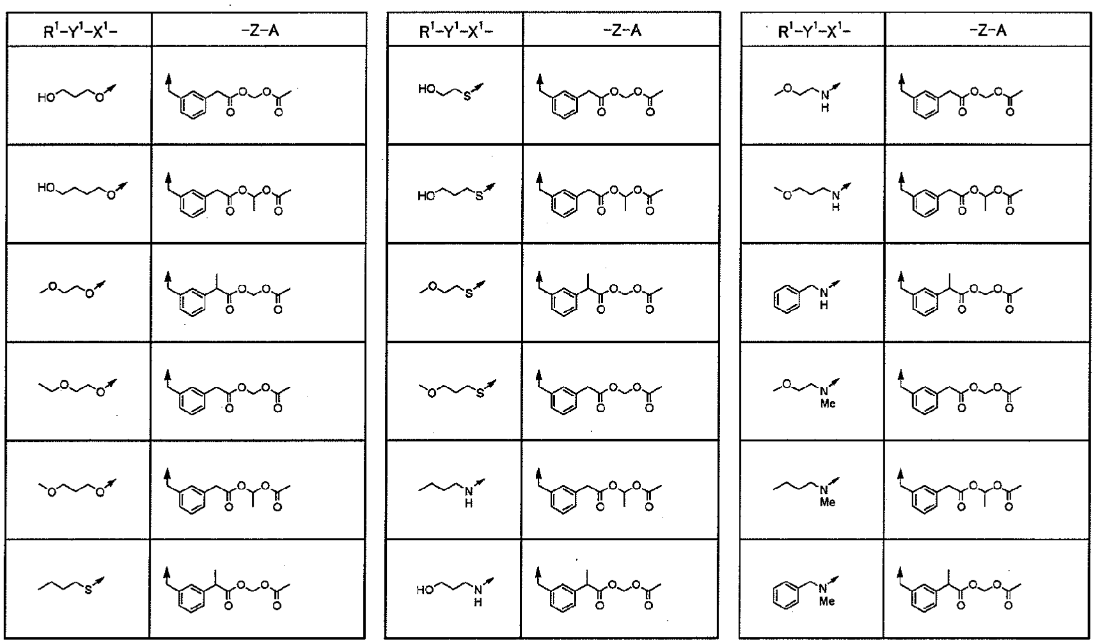
[Table 34]





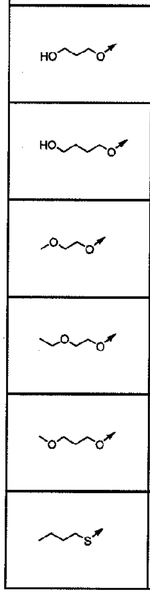
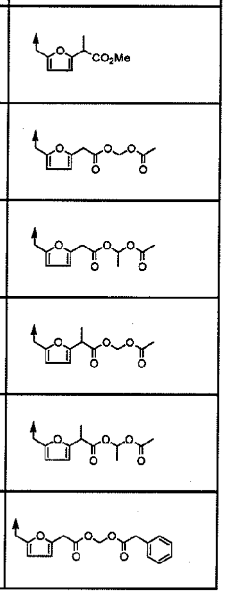
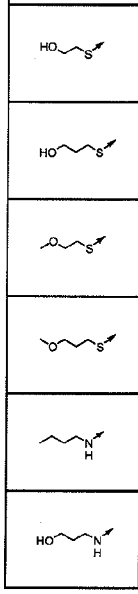
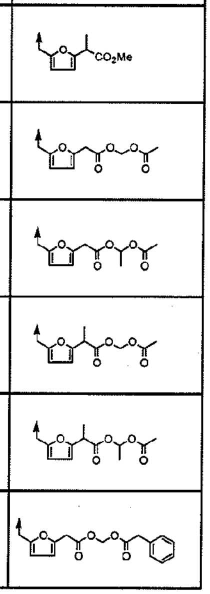
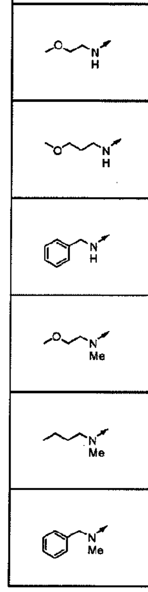
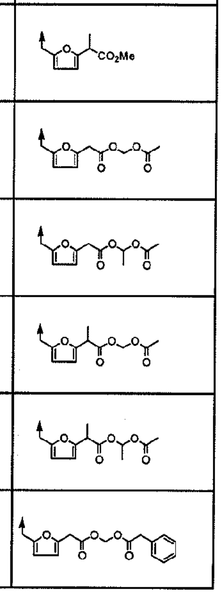
[0098]

[Table 35]



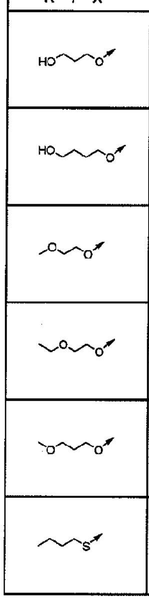
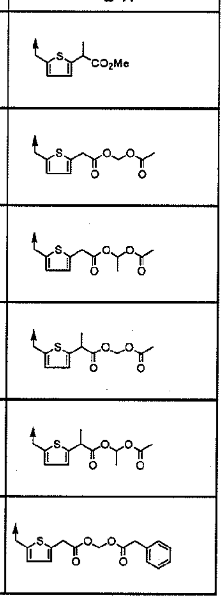
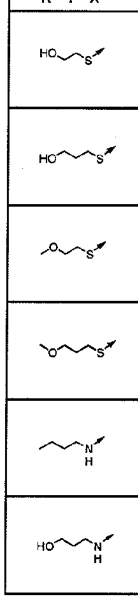
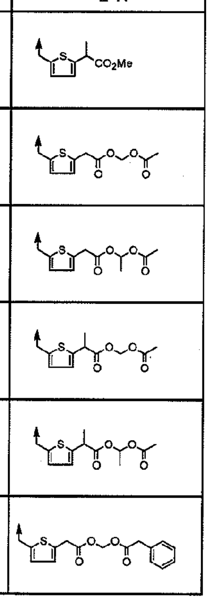
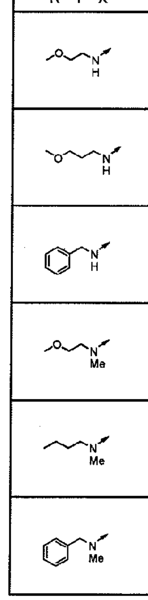
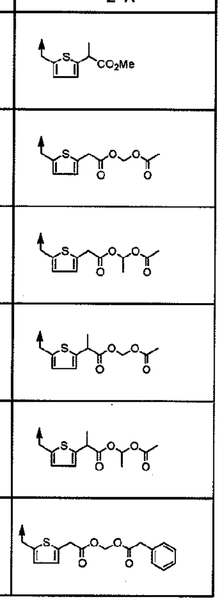
[0099]

[Table 36]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

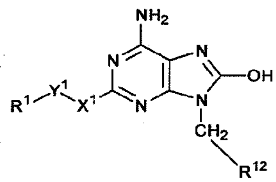
[0100]

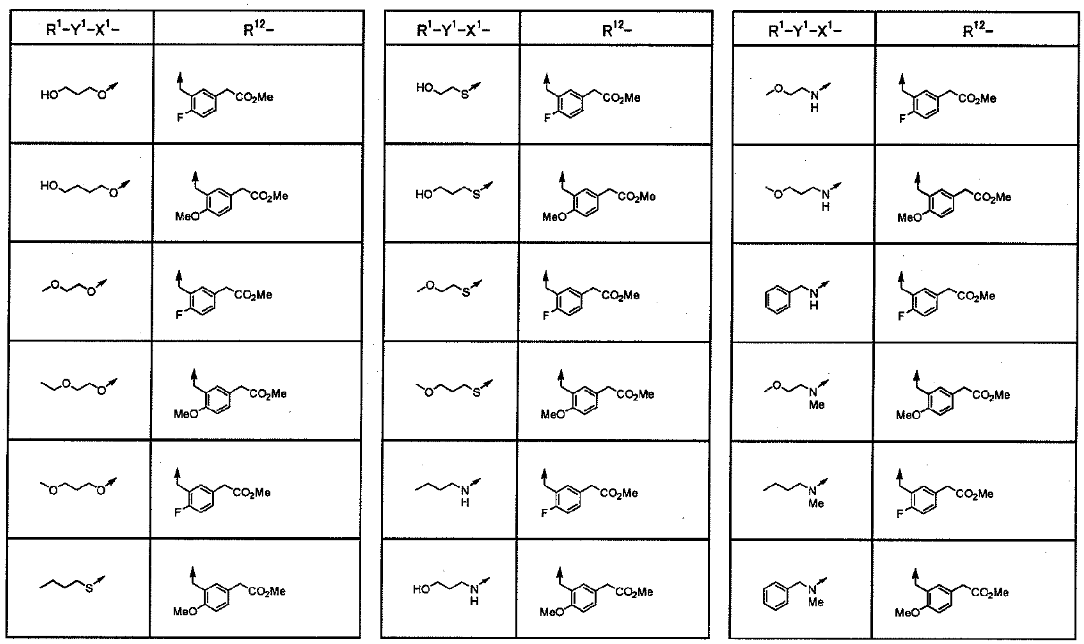
[Table 37]

R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A	R^1-Y^1-X^1-	-Z-A
					

[0101]

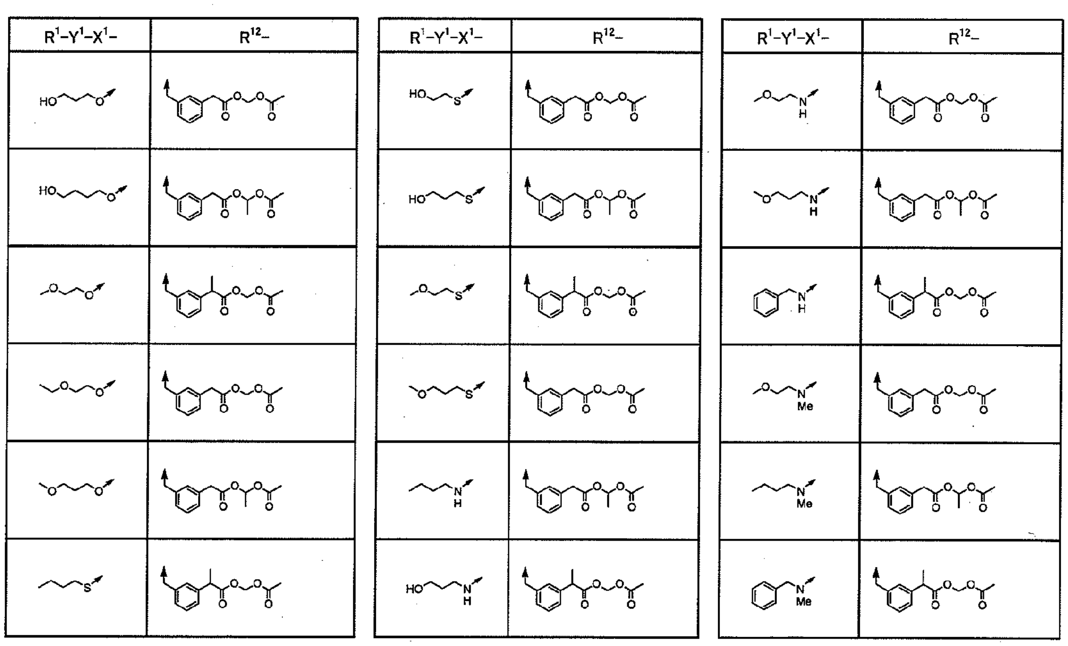
[Table 38]





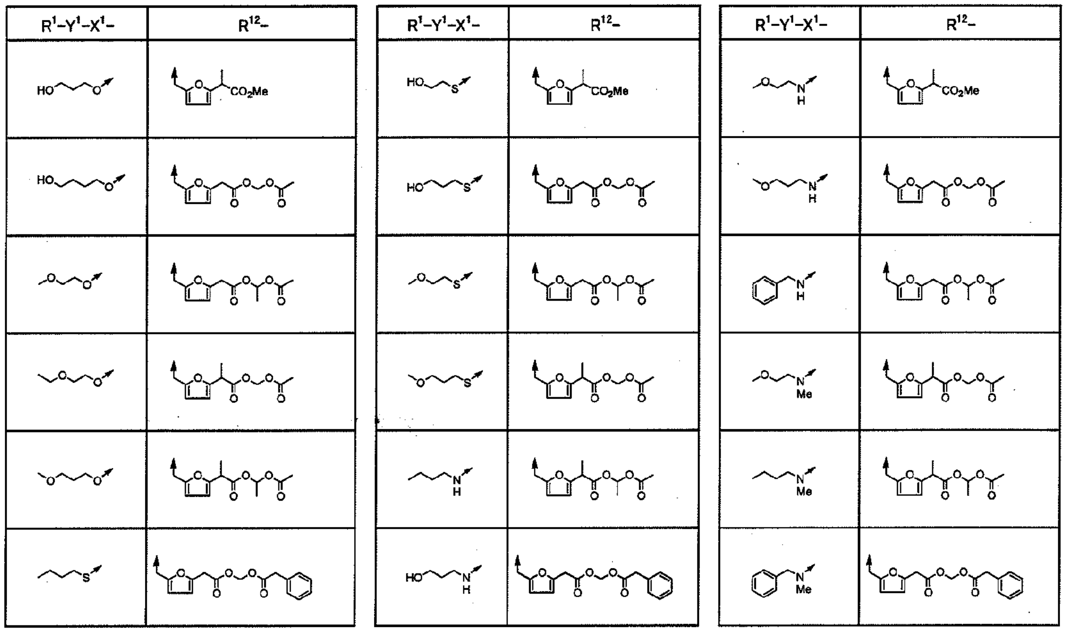
[0102]

[Table 39]



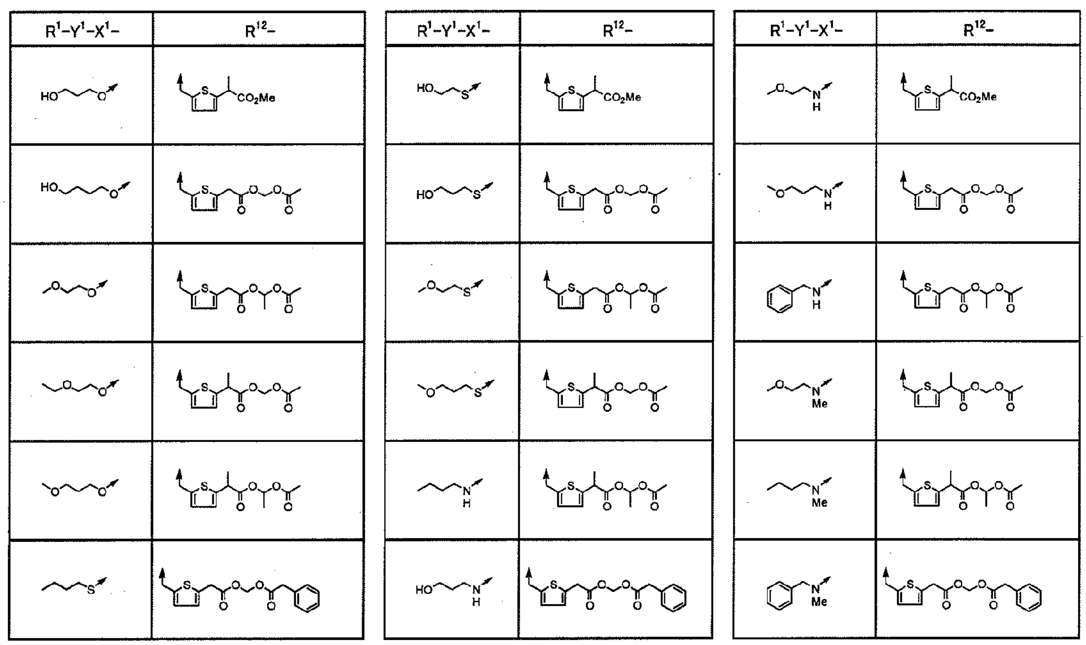
[0103]

[Table 40]



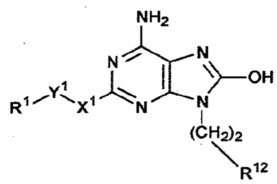
[0104]

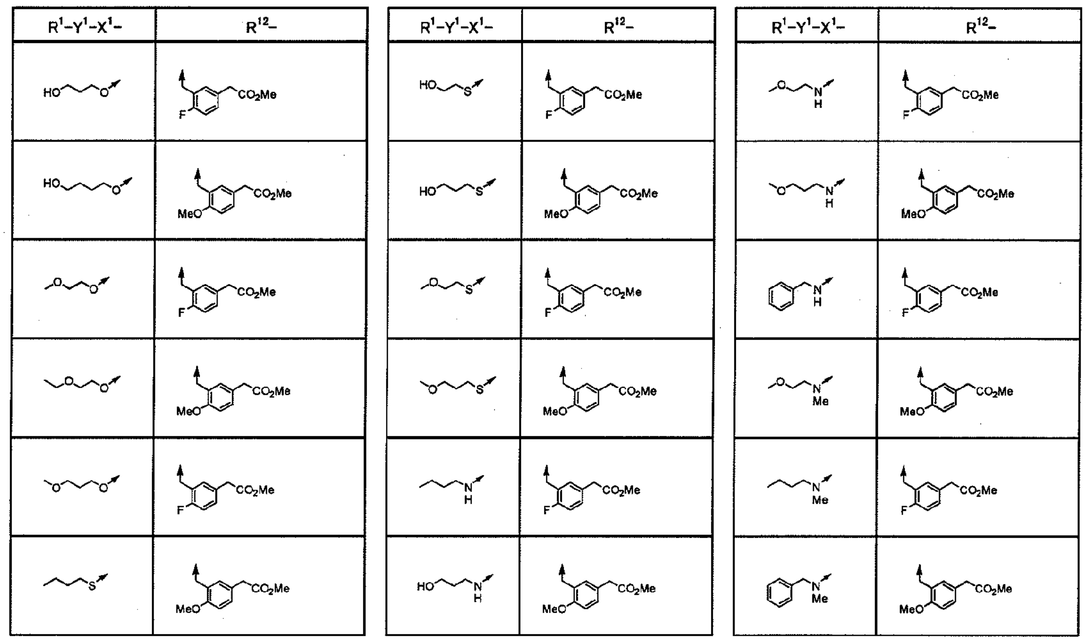
[Table 41]



[0105]

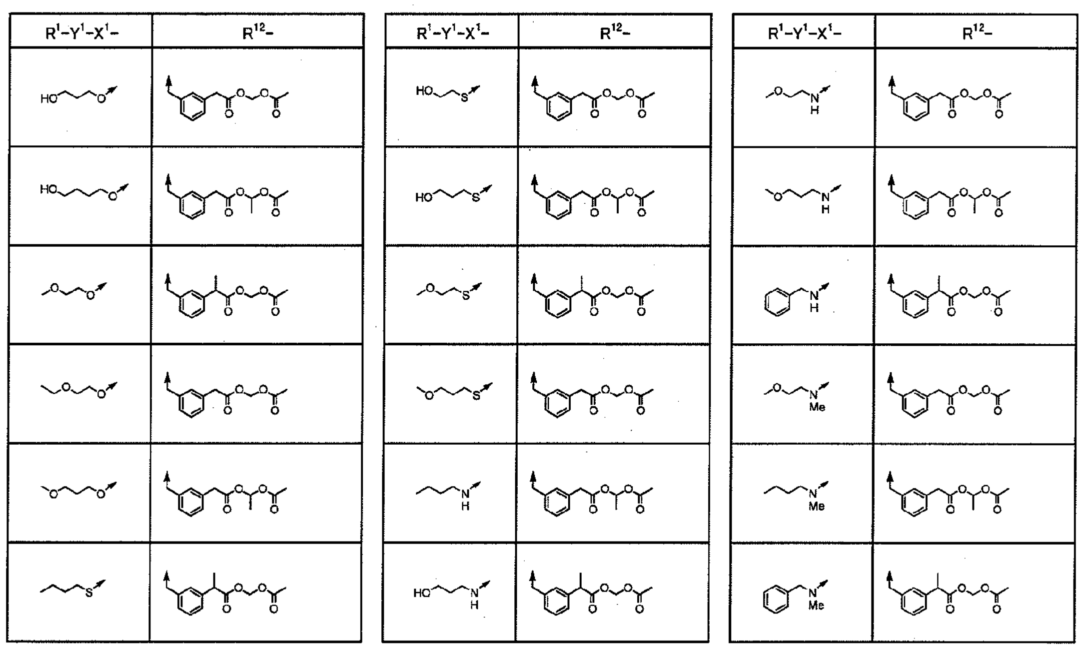
[Table 42]





[0106]

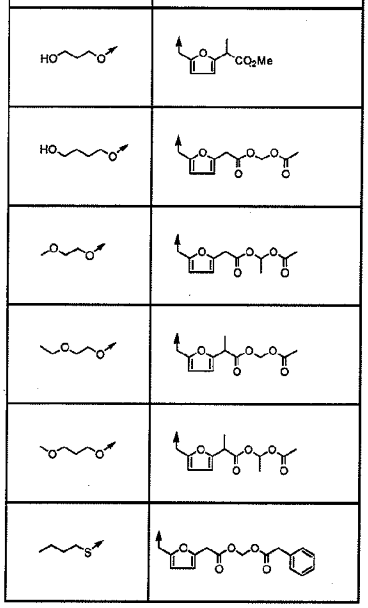
[Table 43]



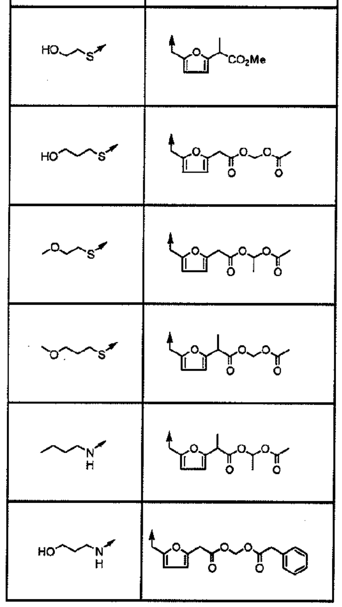
[0107]

[Table 44]

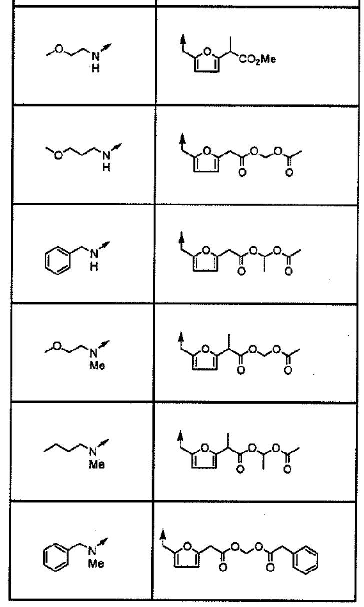
R^1-Y^1-X^1-	R^{12}-



R^1-Y^1-X^1-	R^{12}-



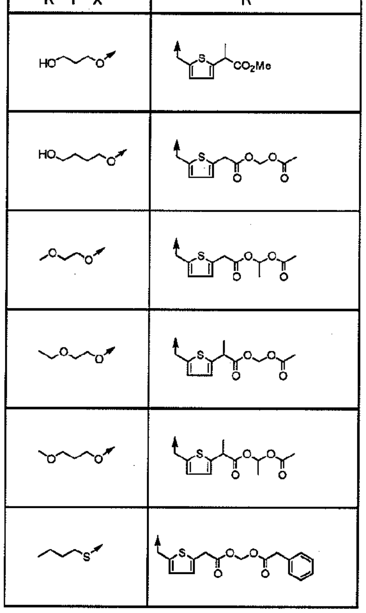
R^1-Y^1-X^1-	R^{12}-



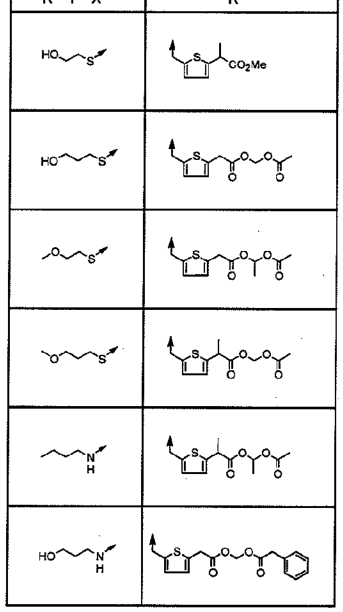
[0108]

[Table 45]

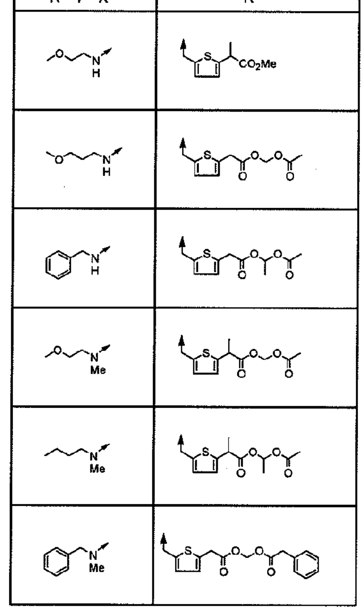
R^1-Y^1-X^1-	R^{12}-



R^1-Y^1-X^1-	R^{12}-

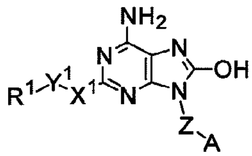


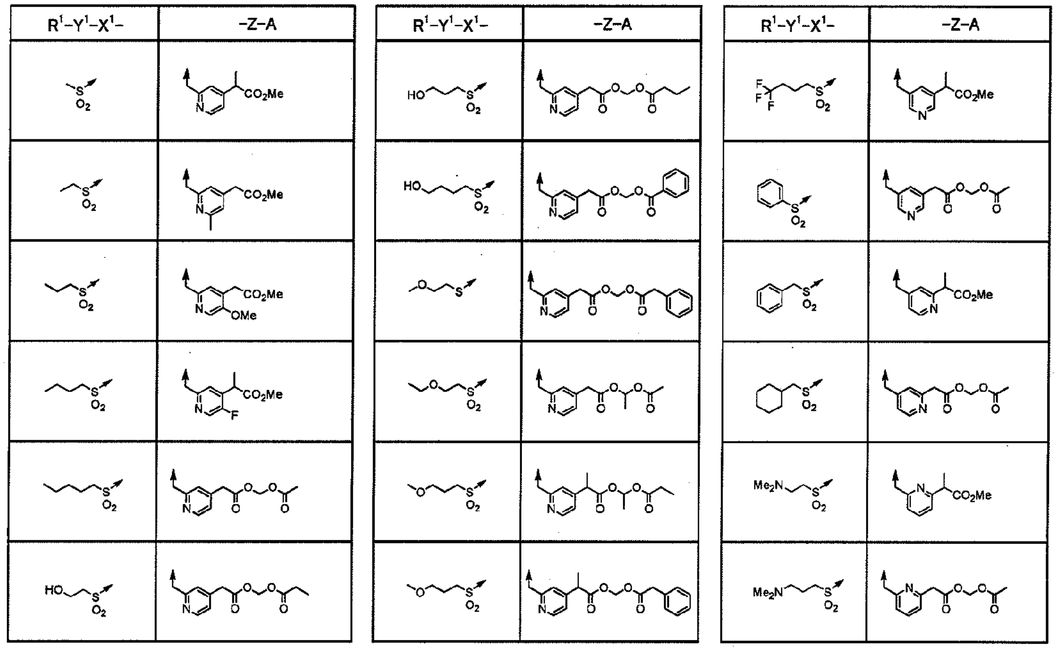
R^1-Y^1-X^1-	R^{12}-



[0109]

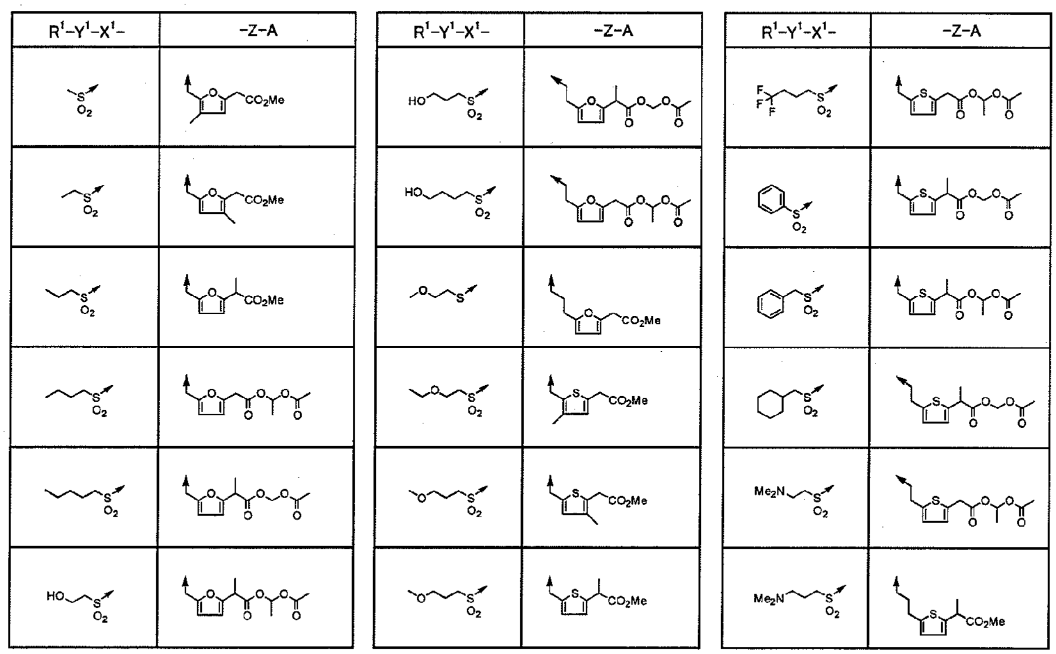
[Table 46]





[0110]

[Table 47]



The present invention is further explained below in details referring to Examples and Reference Examples, but the present invention is not limited thereto. In the following Examples, the chemical structures of the compounds

are expressed in a form of 8-hydroxy type for convenience, but those are not intended to be different from the form of 8-oxo type.

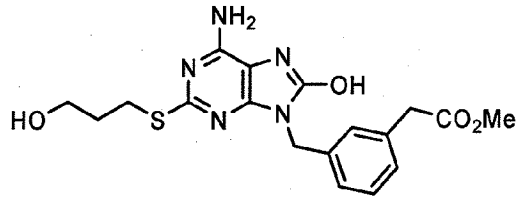
[Example 1]

[0111]

Synthesis of 8-hydroxy-2-(3-hydroxypropylthio)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0112]

[Chemical formula 10]



The titled compound was prepared by the same procedure as described in Reference Example 4, as a white solid. Yield: 97 %.

^{1}H NMR(DMSO-d_6)δ 10.11(1H, s), 7.22(4H, m), 6.58(2H, brs), 4.86(2H, s), 4.51(1H, t, J = 5.2 Hz), 3.65(2H, s), 3.59(3H, s), 3.48(2H, m), 3.05(2H, t. J = 6.9 Hz), 1.78(2H, m).

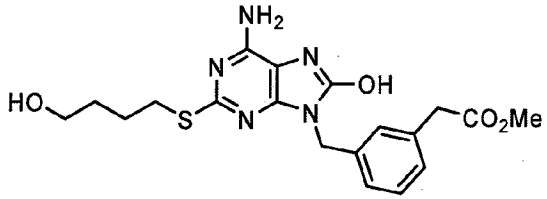
[Example 2]

[0113]

Synthesis of 8-hydroxy-2-(4-hydroxybutylthio)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0114]

[Chemical formula 11]



The titled compound was prepared by the same procedure as described in Reference Example 4, as a white solid. Yield: 24 %.

^{1}H NMR(DMSO-d_6)δ 10.08(1H, s), 7.20(4H, m), 6.50(2H, brs), 4.85(2H, s), 4.38(1H, t, J = 5.1 Hz), 3.64(2H, s), 3.58(3H, s), 3.37(2H, m), 3.01(2H, t, J = 6.8 Hz), 1.64(2H, m), 1.50(2H, m).

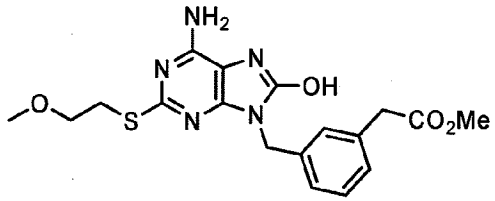
[Example 3]

[0115]

Synthesis of 8-hydroxy-2-(2-methoxyethylthio)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0116]

[Chemical formula 12]



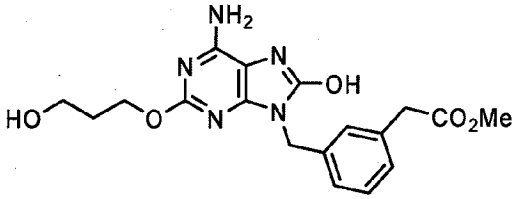
The titled compound was prepared by the same procedure as described in Reference Example 4, as a white solid. Yield: 84 %.
^{1}H NMR(DMSO-d_6)δ 10.12(1H, s), 7.21(4H, m), 6.56(2H, brs), 4.86(2H, s), 3.66(2H, s), 3.59(3H, s), 3.52(2H, t, J = 6.6 Hz), 3.22(3H, s), 3.20(2H, t, J = 6.6 Hz).
[Example 4]

[0117]

Synthesis of 8-hydroxy-2-(3-hydroxypropoxy)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0118]

[Chemical formula 13]



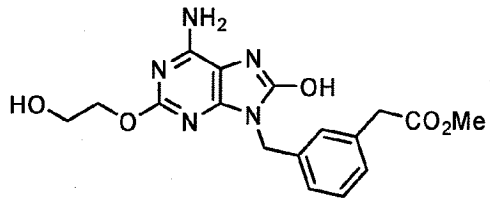
8-Bromo-2-(3-hydroxypropoxy)-9-(3-methoxycarbonylmethylbenzyl)-adenine (0.43 g, 0.96 mmol) prepared in Reference Example 5 was suspended in a mixture of a 5N aqueous sodium hydroxide solution (8 ml) and methanol (5 ml), and the mixture was stirred at 100°C for 9 hours. After neutralizing with 12N hydrochloric acid and concentrating, methanol (30 ml) and conc. sulfuric acid (3 ml) were added thereto. After refluxing for 5 hours, the mixture was neutralized with a saturated aqueous sodium bicarbonate solution, extracted with chloroform, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (SiO_2 50 g, elute: $CHCl_3$/MeOH = 100/0~20/1) to give the titled compound as a white solid (0.29 g, 2.41 mmol). Yield: 78 %.
^{1}H NMR(DMSO-d_6)δ9.96(1H, brs), 7.27(1H, t, J = 7.6 Hz), 7.20(1H, s), 7.16(2H, m), 6.46(2H, brs), 4.83(2H, s), 4.49(1H, t, J = 5.1 Hz), 4.19(2H, t, J = 6.5 Hz), 3.65(2H, s), 3.59(3H, s), 3.50(2H, q, J = 6.2 Hz), 1.79(2H, qui, J = 6.4 Hz).
[Example 5]

[0119]

Synthesis of 8-hydroxy-2-(2-hydroxyethoxy)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0120]

[Chemical formula 14]



The titled compound was prepared by the same procedure as described in Example 4, as a white solid. Yield: 83 %.

^{1}H NMR(DMSO-d_6)δ 9.97(1H, s), 7.27(1H, t, J = 7.6 Hz), 7.20(3H, m), 6.47(2H, s), 4.83(2H, s), 4.79(1H, t, J = 5.6 Hz), 4.15(2H, t, J = 4.9 Hz), 3.64(4H, m), 3.59(3H, s).

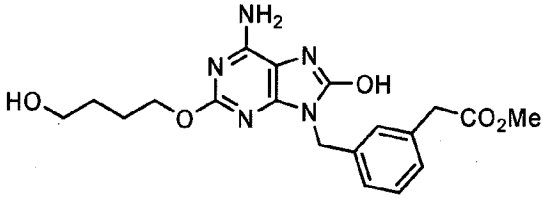
[Example 6]

[0121]

Synthesis of 8-hydroxy-2-(4-hydroxybutoxy)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0122]

[Chemical formula 15]



Using 2-chloro-9-(3-methoxycarbonylmethylbenzyl)adenine prepared in Reference Example 1, the procedures of Reference Example 4, Reference Example 2 and Example 4 were carried out in this order to give the titled compound as a white solid. Yield: 21 %.

^{1}H NMR(DMSO-d_6)δ 9.96(1H, brs), 7.27(1H, t, J = 7.6 Hz), 7.20(3H, m), 6.45(2H, m), 4.83(2H, s), 4.42(1H, t, J = 5.2 Hz), 4.14(2H, t, J = 6.6 Hz), 3.65(2H, s), 3.58(3H, s), 3.41(2H, q, J = 6.4 Hz), 1.67(2H, qui, J = 6.7 Hz), 1.49(2H, qui, J = 6.7 Hz).

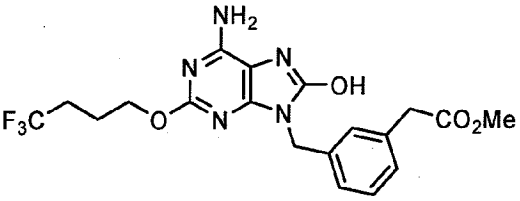
[Example 7]

[0123]

Synthesis of 8-hydroxy-9-(3-methoxycarbonylmethylbenzyl)-2-(4,4,4-trifluoro-butoxy)adenine

[0124]

[Chemical formula 16]



The titled compound was prepared by the same procedure as described in Example 4, as a white solid. Yield: 82 %.

^{1}H NMR(DMSO-d_6)δ 9.97(1H, brs), 7.27(1H, t, J = 7.6 Hz), 7.20(1H, s), 7.16(2H, m), 6.49(2H, brs), 4.84(2H, s), 4.20(2H, t, J = 6.3 Hz), 3.64(2H, s), 3.58(3H, s), 2.35(2H, m), 1.88(2H, m).

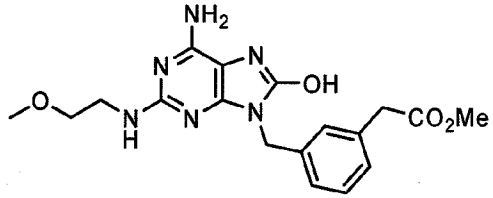
[Example 8]

[0125]

Synthesis of 8-hydroxy-9-(3-methoxycarbonylmethylbenzyl)-2-(N-2-methoxyethyl-amino)adenine

[0126]

[Chemical formula 17]



The titled compound was prepared by the same procedure as described in Example 4 as a white solid. Yield: 54 %.

^{1}H NMR(DMSO-d_6)δ 9.65(1H, s), 7.26(1H, t, J = 7.6 Hz), 7.18(3H, m), 6.15(1H, t, J = 5.5 Hz), 6.05(2H, brs), 4.78(2H, s), 3.64(2H, s), 3.59(3H, s), 3.37(4H, m), 3.22(3H, s).

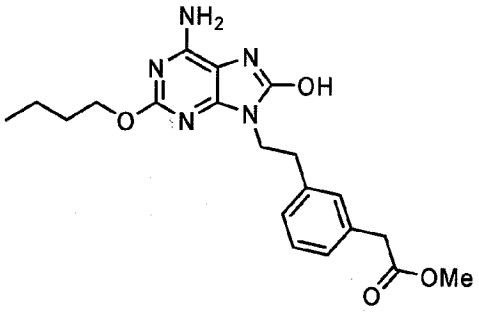
[Example 9]

[0127]

Synthesis of 2-butoxy-8-hydroxy-9-[2-(3-methoxycarbonylmethylphenyl)-ethyl]adenine

[0128]

[Chemical formula 18]



The titled compound was prepared by the same procedure as described in Example 4. Yield: 84 %.

^{1}H NMR(DMSO-d_6)δ 9.85(1H, brs), 7.24-7.20(1H, m), 7.10(1H, s), 7.10-7.08(2H, m), 6.41(2H, brs), 4.14(2H, t, J = 6.6 Hz), 3.88(2H, t, J = 7.6 Hz), 3.62(2H, s), 3.59(3H, s), 2.96(2H, t, J = 7.6 Hz), 1.65(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.39(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.92(3H, t, J = 7.4 Hz).

[Example 10]

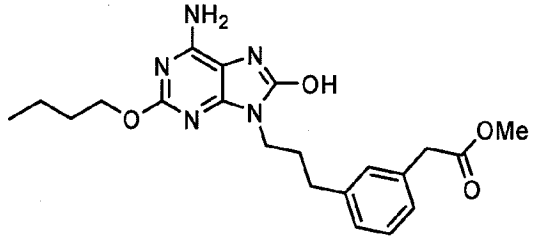
[0129]

Synthesis of 2-butoxy-8-hydroxy-9-[3-(3-methoxycarbonylmethylphenyl)-

propyl]adenine

[0130]

[Chemical formula 19]



Using 8-bromo-2-butoxy-9-[3-(3-cyanomethylphenyl)propyl]adenine prepared in Reference Example 29, the same procedure as in Example 4 was carried out to give the titled compound. Yield: 88 %.

^{1}H NMR(DMSO-d_6)δ 9.84(1H, brs), 7.21(1H, dd, J = 7.5, 7.5 Hz), 7.12-7.05(3H, m), 6.40(2H, brs), 4.31(2H, t, J = 6.6 Hz), 3.70(2H, t, J = 7.0 Hz), 3.62(2H, s), 3.59(3H, s), 2.57(2H, t, J = 7.7 Hz), 1.94(2H, tt, J = 7.7 Hz, 7.0 Hz), 1.63(2H, tt, J = 7.8 Hz, 6.6 Hz), 1.37(2H, tq, J = 7.8 Hz, 7.4 Hz), 0.91(3H, t, J = 7.4 Hz).

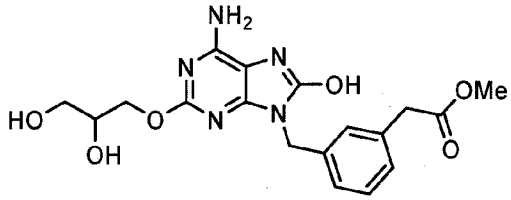
[Example 11]

[0131]

Synthesis of 2-(2,3-dihydroxy-1-propoxy)-8-hydroxy-9-(3-methoxycarbonyl-methylbenzyl)adenine

[0132]

[Chemical formula 20]



The titled compound was prepared by the same procedure as described in Example 4. Yield: 46 %.

^{1}H NMR(DMSO-d_6)δ 9.96(1H, brs), 7.27(1H, dd, J = 7.6, 7.5 Hz), 7.20-7.14(3H, m), 6.47(2H, brs), 4.87(1H, d, J = 5.2 Hz), 4.84(2H, s), 4.61(1H, t, J = 5.6 Hz), 4.16(1H, dd, J = 10.9, 4.4 Hz), 4.03(1H, dd, J = 10.9, 6.4 Hz), 3.76-3.72(1H, m), 3.65(2H, s), 3.59(3H, s), 3.39(2H, dd, J = 5.6, 5.6 Hz).

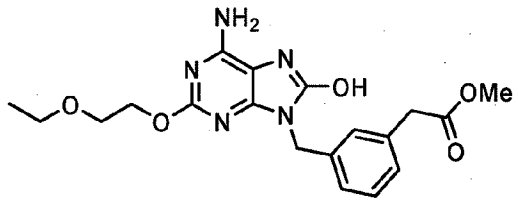
[Example 12]

[0133]

Synthesis of 2-(2-ethoxyethoxy)-8-hydroxy-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0134]

[Chemical formula 21]



The titled compound was prepared by the same procedure as described in Example 4. Yield: 79 %.

^{1}H NMR(DMSO-d_6)δ 9.97(1H, s), 7.27(1H, dd, J = 7.6, 7.5 Hz), 7.20-7.14(3H, m), 6.47(2H, brs), 4.83(2H, s), 4.24(2H, t, J = 4.8 Hz), 3.65(2H, s), 3.61(2H, t, J = 4.8 Hz), 3.58(3H, s), 3.45(2H, q, J = 7.0 Hz), 1.10(3H, t, J = 7.0 Hz).

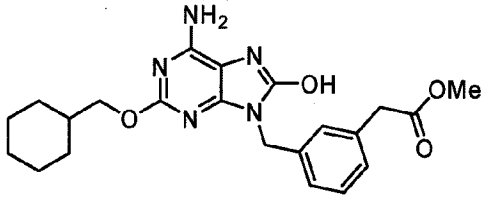
[Example 13]

[0135]

Synthesis of 2-cyclohexylmethoxy-8-hydroxy-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0136]

[Chemical formula 22]



The titled compound was prepared by the same procedure as described in Example 4. Yield: 85 %.

^{1}H NMR(DMSO-d_6)δ 9.94(1H, s), 7.27(1H, dd, J = 7.7, 7.5 Hz), 7.20-7.15(3H, m), 6.45(2H, brs), 4.83(2H, s), 3.95(2H, d, J = 6.4 Hz), 3.64(2H, s), 3.58(3H, s), 1.75-1.61(6H, m), 1.23-1.11(3H, m), 0.99-0.93(2H, m).

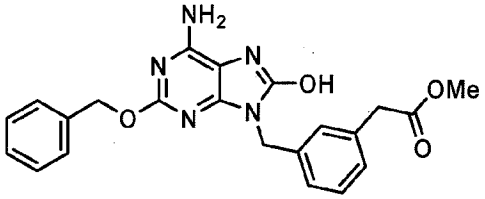
[Example 14]

[0137]

Synthesis of 2-benzyloxy-8-hydroxy-9-(3-methoxycarbonylmethylbenzyl)adenine

[0138]

[Chemical formula 23]



The titled compound was prepared by the same procedure as described in Example 4. Yield: 59 %

^{1}H NMR(DMSO-d_6)δ 10.01(1H, brs), 7.42-7.40(2H, m), 7.36-7.16(5H, m), 7.16-7.14(2H, m), 6.53(2H, brs), 5.24(2H, s), 4.83(2H, s), 3.62(2H, s), 3.57(3H, s).

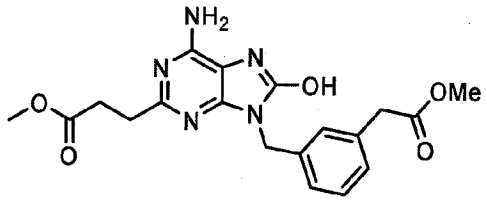
[Example 15]

[0139]

Synthesis of 8-hydroxy-2-(2-methoxycarbonylethyl)-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0140]

[Chemical formula 24]



The titled compound was prepared by the same procedure as described in Example 4. Yield: 50 %

^{1}H NMR(DMSO-d_6)δ 10.15(1H, brs), 7.26(1H, dd, J = 7.6, 7.6 Hz), 7.23(1H, s), 7.18-7.14(2H, m), 6.39(2H, brs), 4.85(2H, s), 3.65(2H, s), 3.59(3H, s), 3.53(3H, s), 2.87(2H, t, J = 7.2 Hz), 2.70(2H, t, J = 7.2 Hz).

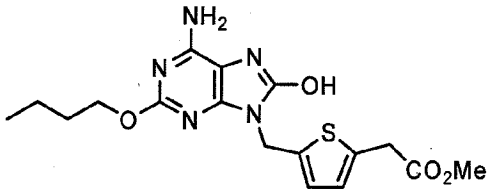
[Example 16]

[0141]

Synthesis of 2-butoxy-8-hydroxy-9-{(5-methoxycarbonylmethyl-2-thienyl)-methyl}adenine

[0142]

[Chemical formula 25]



Using 2-butoxy-8-hydroxy-9-{(5-hydroxymethyl-2-thienyl)methyl}adenine prepared in Reference Example 44, the procedures of Reference Example 18, Reference Example 19 and Reference Example 20 were carried out in this order to give the titled compound as a white solid. Yield: 49 %

^{1}H NMR(DMSO-d_6)δ 9.95(1H, s), 6.90(1H, d, J = 3.5 Hz), 6.78(1H, d, J = 3.5 Hz), 6.46(2H, brs), 4.94(2H, s), 4.17(2H, t, J = 6.6 Hz), 3.85(2H, s), 3.61(3H, s), 1.65(2H, 5, J = 6.6 Hz), 1.38(2H, 6, J = 7.4 Hz), 0.92(3H, t, J = 7.3Hz).

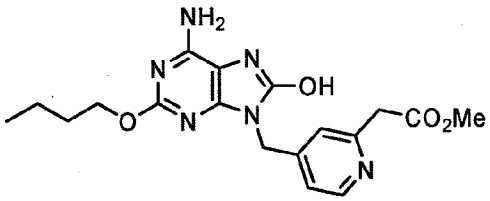
[Example 17]

[0143]

Synthesis of 2-butoxy-8-hydroxy-9-{(2-methoxycarbonylmethyl-4-pyridyl)-methyl}adenine

[0144]

[Chemical formula 26]



The titled compound was prepared by the same procedure as described in Example 16, as a white solid. Yield: 19 %

^{1}H NMR(DMSO-d_6)δ 10.03(1H, brs), 8.42(1H, d, J = 5.0 Hz), 7.20(1H, s), 7.12(1H, dd, J = 1.4 Hz, 5.1 Hz), 6.52(2H, brs), 4.88(2H, s), 4.10(2H, t, J = 6.6 Hz), 3.82(2H, s), 3.59(3H, s), 1.59(2H, 5, J = 6.6 Hz), 1.35(2H, 6, J = 7.3 Hz), 0.88(3H, t, J = 7.3 Hz).

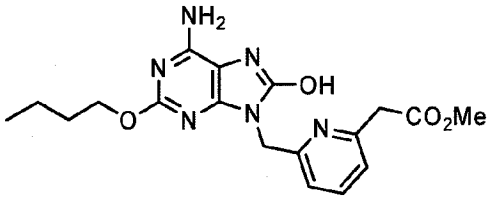
[Example 18]

[0145]

Synthesis of 2-butoxy-8-hydroxy-9-{(6-methoxycarbonylmethyl-2-pyridyl)methyl}-adenine

[0146]

[Chemical formula 27]



The titled compound was prepared by the same procedure as described in Reference Example 20 as a white solid. Yield: 34 %.

^{1}H NMR(DMSO-d_6)δ 9.99(1H, brs), 7.70(1H, t, J = 7.8 Hz), 7.24(1H, d, J = 7.6 Hz), 6.96(1H, d, J = 7.7 Hz), 6.47(2H, brs), 4.91(2H, s), 4.14(2H, t, J = 6.6 Hz), 3.81(2H, s), 3.58(3H, s), 1.57(2H, 5, J = 6.6 Hz), 1.37(2H, 6, J = 7.4 Hz), 0.85(3H, t, J = 7.3 Hz).

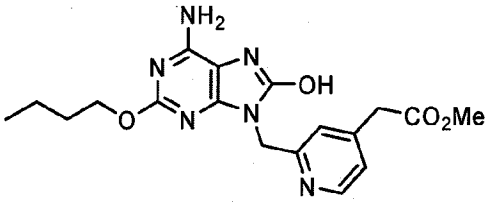
[Example 19]

[0147]

Synthesis of 2-butoxy-8-hydroxy-9-{(4-methoxycarbonylmethyl-2-pyridyl)methyl}-adenine

[0148]

[Chemical formula 28]



Using 8-bromo-2-butoxyadenine (525 mg, 1.83 mmol) prepared in Reference Example 54, the alkylation was carried out in the same manner as described in Reference Example 1, and then the same procedure as described in

Reference Example 3 was carried out to give the titled compound as a white solid. Yield 14 %

^{1}H NMR(DMSO-d_6)δ 9.94(1H, s), 8.39(1H, d, J = 5.0 Hz), 7.18(1H, d, J = 5.0 Hz), 7.14(1H, s), 6.45(2H, brs), 4.94(2H, s), 4.07(2H, t, J = 6.6 Hz), 3.73(2H, s), 3.60(3H, s), 1.57(2H, 5, J = 6.6 Hz), 1.33(2H, 6, J = 6.8 Hz), 0.87(3H, t, J = 7.3 Hz).

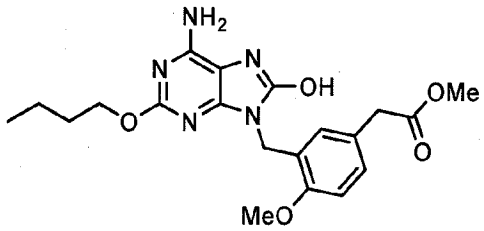
[Example 20]

[0149]

Synthesis of 2-butoxy-8-hydroxy-9-(2-methoxy-5-methoxycarbonylmethyl)benzyl-adenine

[0150]

[Chemical formula 29]



The titled compound was prepared by the same procedure as described in Example 10, as a white solid. Yield: 93 %

^{1}H NMR(DMSO-d_6)δ 10.00(1H, brs), 7.13(1H, d, J = 8.4 Hz), 6.97(1H, d, J = 8.4 Hz), 6.67(1H, s), 6.47(2H, brs), 4.80(2H, s), 4.08(2H, t, J = 6.6 Hz), 3.83(3H, s), 3.53(3H, s), 3.50(2H, s), 1.59(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.33(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.87(3H, t, J = 7.4 Hz).

The aerosol solution containing the above component is prepared.

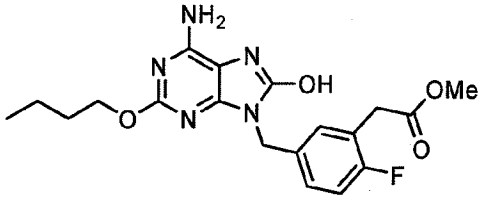
[Example 21]

[0151]

Synthesis of 2-butoxy-9-(4-fluoro-3-methoxycarbonylmethyl)benzyl-8-hydroxy-adenine

[0152]

[Chemical formula 30]



The titled compound was prepared by the same procedure as described in Example 10 as a white solid. Yield: 93 %

^{1}H NMR(DMSO-d_6)δ 9.96(1H, s), 7.29-7.23(2H, m), 7.14(1H, dd, J = 9.7, 8.4 Hz), 6.46(2H, brs), 4.82(2H, s), 4.14(2H, t, J = 6.6 Hz), 3.70(2H, s), 3.60(3H, s), 1.62(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.37(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.90(3H, t, J = 7.4 Hz).

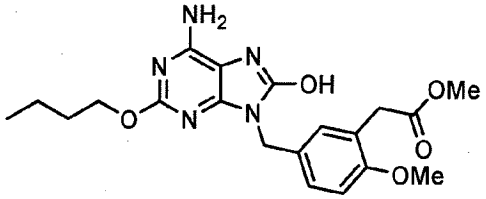
[Example 22]

[0153]

Synthesis of 2-butoxy-8-hydroxy-9-(4-methoxy-3-methoxycarbonylmethyl-phenyl)methyladenine

[0154]

[Chemical formula 31]



Using methyl 3-bromomethyl-6-methoxyphenylacetate prepared in Reference Example 75 and 2-butoxyadenine, the procedures of Reference Example 1, Reference Example 2 and Example 4 were carried out in this order to give the titled compound as a white solid.

^{1}H NMR($CDCl_3$)δ 9.91(1H, s), 7.20(1H, d, J = 8.4 Hz), 7.15(1H, s), 6.91(1H, d, J = 8.4 Hz), 6.42(2H, brs), 4.75(2H, s), 4.15(2H, t, J = 6.4 Hz), 3.70(3H, s), 3.55(3H, s),3.53(2H, s), 1.62(2H, 5, J = 6.8 Hz), 1.37(2H, 6, J = 7.5 Hz), 0.90(3H, t, J = 7.3 Hz).

[Example 23]

[0155]

Interferon inducing activity in rat spleen cells (in vitro)

Spleen was removed from CD(SD)IGS rats (male; 8-10 weeks old). A suspension of spleen cells of $1x10^7$ cells/ml was prepared by using MEM broth containing non serum, and each 0.1 ml thereof was poured in each well of a 96-well microplate. Then, a test compound diluted with the same broth (containing 0.2 % DMSO) was poured in an amount of 0.1 ml to each well and incubated in 5 % CO_2 incubator at 37°C for 24 hours. The culture broth was centrifuged to give a culture supernatant. The interferon activity in the culture supernatant was quantitatively measured by the partially-improved bioassay method described in J. A. Armstrong, Methods in Enzymology 78, 381-7. Namely, after mouse fibroblast L929 in 4×10^4 cells/50 μl was cultured in a 96-well culture plate for 7 hours, thereto was added 50 μl of the diluted culture supernatant and the mixture was further cultured for 17 hours. After the cultured broth in each well was removed, each 100 μl of vesicular stomatitis virus was added to each well, and the effect of the cell denaturation at 44 hours after the virus infection was confirmed by the neutral red stain. In Table 46, an interferon inducing activity (minimum effective concentration) of each compound is shown.

[0156]

[Table 48]

Compound	Minimum effective concentration (nM)	Compound	Minimum effective concentration (nM)
Example 1	10	Comparative Example 1	>1000
Example 2	10	Comparative Example 2	1000
Example 4	30	Comparative Example 4	>1000
Example 5	100	Comparative Example 5	>1000
Example 9	30	Comparative Example 9	300
Example 10	10	Comparative Example 10	100
Example 11	100	Example 11	>1000
Example 12	10	Example 12	>1000
Example 13	30	Example 13	100
Example 15	3	Example 15	1000
Example 16	1	Example 16	3
Example 18	3	Example 18	10
Example 19	3	Example 19	30
Example 20	0.1	Example 20	10
Example 21	1	Example 21	30
Example 22	3	Example 22	10

[Example 24]

[0157]

Metabolic stability test using human plasma

Plasma was prepared from fresh human blood and a test compound (containing 1 % DMSO) of the final concentration of 1 μM was added thereto.

After a metabolic reaction by plasma esterase was conducted at 37°C for 15 minutes, the test compound was extracted with ethyl acetate, and quantitatively analyzed by reverse phase HPLC. The metabolic stability of the test compound was shown by the residual amount (%) when the concentration of said compound prior to metabolization was regarded as 100 %. The results are shown in Table 49.

[0158]

[Table 49]

Compound	Residual rate (%)
Example 1	<1
Example 2	<1
Example 4	3.2
Example 5	5.8
Example 9	7.9
Example 10	<1
Example 11	20.9
Example 12	4.1
Example 13	29.6
Example 15	<1
Example 16	5.2
Example 19	11.4

[Example 25]

[0159]

Example 25: Metabolic stability test on rat liver S9

The reaction using rat liver S9 was conducted on a 96-well plate by using a screening robot by Tecan Company. An S9 solution was prepared by adding 250 mM Kpi (pH 7.4, 20 ml) and deionized water (20 ml) to rat liver S9 (10 ml). A Cofactor solution was prepared by dissolving NADPH (220 mg) in deionized water (40.5 ml, Final 6 mM), and an IS (Internal Standard) solution was prepared by adding an IS solution (1 mM DMSO solution, 300 µl) to acetonitrile (30 ml, 100 times dilution). A test compound (1 µM DMSO solution) was dissolved in an incubator at 37°C. After each 35 µL thereof was poured into a 96-well plate (24 samples/plate), the plates (sample plates, 96-well plates for dilution, each Deep well plate for the reaction and the recovery, plates for extraction of a solid phase) and the reagents (S9 solution, Cofactor solution, IS (Internal Standard) solution, Stop solution, acetonitrile for elution) were set to the specified position in the booth of the robot, and the reaction started (the concentration of the test compounds was 1 µM). Incubation was conducted under shaking at 37°C, the solid phase was extracted (at the same time, the internal standard for analysis was added). To the recovered samples 200 µL/well was added 50 µL of acetonitrile per each well, and to 2 FALCON Deep well plates were poured 100 µL/well of the solution per well. By subjecting to the LC/MS analysis, the chromatography of the test compound and the internal standard were described and the peak area was calculated. And then, the stability (residual rate after reaction) was calculated. The results are shown in Table 50.

[0160]

[Table 50]

Compound	Residual rate (%)
Example 4	8
Example 9	0
Example 10	1
Example 12	0
Example 13	11
Example 15	0
Example 16	0
Example 17	3
Example 18	0
Example 19	0
Example 20	0
Example 21	1
Example 22	2

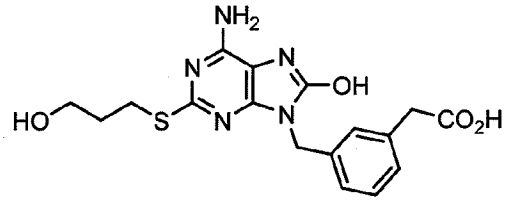
[Example 26]

[0161]

Comparative Example 1: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(3-hydroxypropylthio)adenine

[0162]

[Chemical formula 32]



8-Hydroxy-2-(3-hydroxypropylthio)-9-(3-methoxycarbonylmethyl-benzyl)adenine (50 mg, 0.124 mmol) prepared in Example 1 was added to a mixture of 1N aqueous sodium hydroxide solution (10 ml) and methanol (10 ml), and the mixture was stirred at room temperature for 2 hours. After neutralization with conc. hydrochloric acid, methanol was removed by evaporation. The precipitated solid was taken by filtration to give the titled compound as a white solid (47 mg, 0.121 mmol). Yield: 97 %

^{1}H NMR(DMSO-d_6)δ 7.18(4H, m), 6.82(2H, brs), 4.83(2H, s), 3.49(2H, t, J = 6.3 Hz), 3.34(2H, s), 3.06(2H, t, J = 6.9 Hz), 1.78(2H, m).

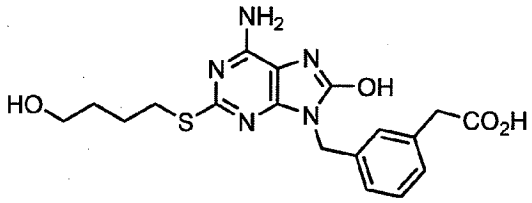
[Example 27]

[0163]

Comparative Example 2: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(4-hydroxybutylthio)adenine

[0164]

[Chemical formula 33]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 70 %

^{1}H NMR(DMSO-d_6)δ 12.46(1H, brs), 10.12(1H, s), 7.24(4H, m), 6.52(2H, brs), 4.89(2H, s), 3.52(2H, s), 3.39(2H, t, J = 6.4 Hz), 3.02(2H, t, J = 7.2 Hz), 1.65(2H, m), 1.52(2H, m).

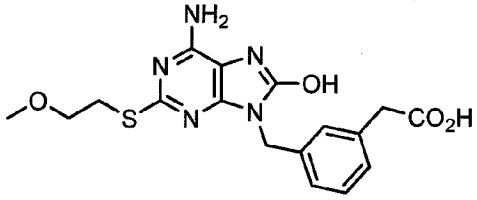
[Example 28]

[0165]

Comparative Example 3: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(2-methoxyethylthio)adenine

[0166]

[Chemical formula 34]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 32 %

^{1}H NMR(DMSO-d_6)δ 7.01(4H, m), 6.56(2H, brs), 4.73(2H, s), 3.41(2H, t, J = 6.7 Hz), 3.21(2H, s), 3.14(3H, s)3.08(2H, t, J = 6.7 Hz).

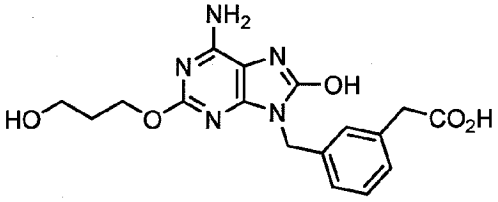
[Example 29]

[0167]

Comparative Example 4: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(3-hydroxypropoxy)adenine

[0168]

[Chemical formula 35]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 82 %

^{1}H NMR(DMSO-d_6)δ 12.29(1H, brs), 9.96(1H, brs), 7.26(1H, t, J = 7.6 Hz), 7.20(1H, s), 7.16(2H, m), 6.46(2H, brs), 4.83(2H, s), 4.50(1H, brs), 4.20(2H, t, J = 6.5 Hz), 3.51(4H, m), 1.79(2H, qui, J = 6.4 Hz).

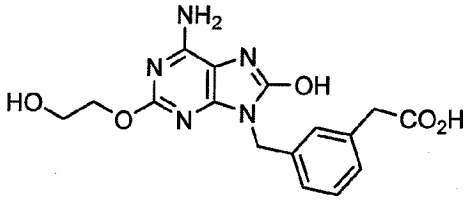
[Example 30]

[0169]

Comparative Example 5: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(2-hydroxyethoxy)adenine

[0170]

[Chemical formula 36]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 70 %

^{1}H NMR(DMSO-d_6)δ 10.03(1H, s), 7.26(1H, t, J = 7.8 Hz), 7.18(3H, m), 6.48(2H, s), 4.83(2H, s), 4.15(2H, t, J = 4.9 Hz), 3.64(2H, t, J = 5.0 Hz), 3.53(2H, s).

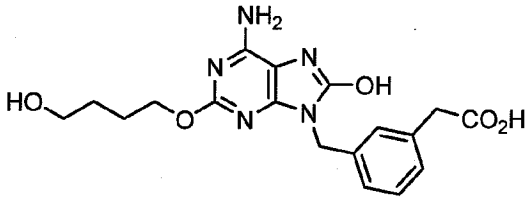
[Example 31]

[0171]

Comparative Example 6: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(4-hydroxybutoxy)adenine

[0172]

[Chemical formula 37]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 62 %

^{1}H NMR(DMSO-d_6)δ 10.37(1H, brs), 7.27(2H, m), 7.12(2H, m), 6.55(2H, m), 4.81(2H, s), 4.15(2H, t, J = 6.6 Hz), 3.39(4H, m), 1.67(2H, qui, J = 6.8 Hz), 1.49(2H, qui, J = 6.7 Hz).

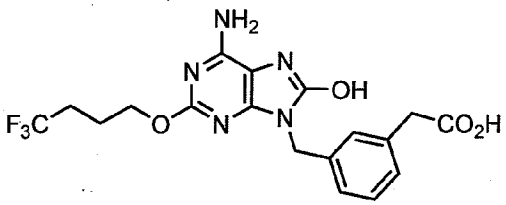
[Example 32]

[0173]

Comparative Example 7: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(4,4,4-trifluorobutoxy)adenine

[0174]

[Chemical formula 38]



The titled compound was prepared in the same method as in

Comparative Example 1 as a white solid. Yield: 88 %
^{1}H NMR(DMSO-d_6)δ12.37(1H, brs), 10.00(1H, brs), 7.26(1H, t, J = 7.8 Hz), 7.21(1H, s), 7.16(2H, m), 6.50(2H, brs), 4.84(2H, s), 4.20(2H, t, J = 6.3 Hz), 3.52(2H, s), 2.36(2H, m), 1.88(2H, m).

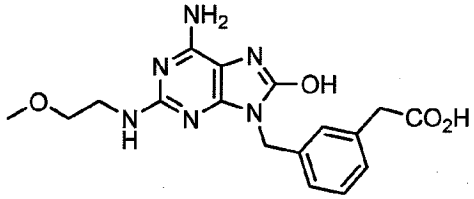
[Example 33]

[0175]

Comparative Example 8: Synthesis of 9-(3-carboxymethylbenzyl)-8-hydroxy-2-(N-2-methoxyethylamino)adenine

[0176]

[Chemical formula 39]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 84 %
^{1}H NMR(DMSO-d_6)δ9.72(1H, s), 7.25(1H, t, J = 7.6 Hz), 7.18(3H, m), 6.14(1H, t, J = 5.1 Hz), 6.07(2H, brs), 4.78(2H, s), 3.52(2H, s), 3.37(4H, m), 3.22(3H, s).

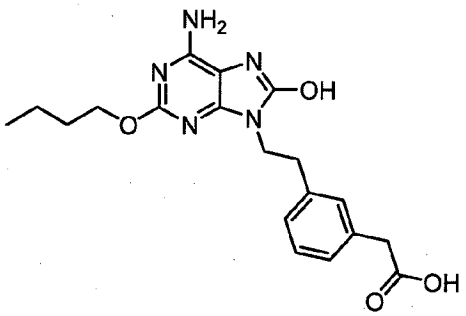
[Example 34]

[0177]

Comparative Example 9: Synthesis of 2-butoxy-9-[2-(3-carboxymethylphenyl)-ethyl]-8-hydroxyadenine

[0178]

[Chemical formula 40]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 87%
^{1}H NMR(DMSO-d_6)δ 12.27(1H, brs), 9.91(1H, s), 7.21(1H, dd, J = 7.5, 7.5 Hz), 7.11(1H, s), 7.10-7.05(2H, m), 6.42(2H, brs), 4.15(2H, t, J = 6.6 Hz), 3.87(2H, t, J = 7.6 Hz), 3.50(2H, s), 2.95(2H, t, J = 7.6 Hz), 1.66(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.39(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.92(3H, t, J = 7.4 Hz).

[Example 35]

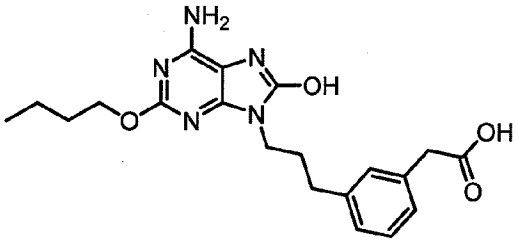
[0179]

Comparative Example 10: Synthesis of 2-butoxy-9-[3-(3-carboxymethylphenyl)-

propyl]-8-hydroxyadenine

[0180]

[Chemical formula 41]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 80 %

^{1}H NMR(DMSO-d_6)δ 12.32(1H, brs), 10.09(1H, brs), 7.18(1H, dd, J = 7.9, 7.8 Hz), 7.08-7.04(3H, m), 6.46(2H, brs), 4.13(2H, t, J = 6.6 Hz), 3.70(2H, t, J = 7.0 Hz), 3.47(2H, s), 2.56(2H, t, J = 7.7 Hz), 1.94(2H, tt, J = 7.7 Hz, 7.0 Hz), 1.63(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.38(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.91(3H, t, J = 7.4 Hz).

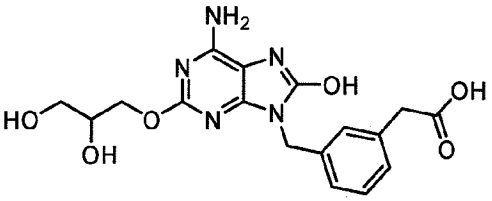
[Example 36]

[0181]

Comparative Example 11: Synthesis of 9-(3-carboxymethylbenzyl)-2-(2,3-dihydroxy-1-propoxy)-8-hydroxyadenine

[0182]

[Chemical formula 42]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 76 %

^{1}H NMR(DMSO-d_6)δ 9.99(1H, brs), 7.26(1H, dd, J = 8.0, 7.1 Hz), 7.20(1H, s), 7.16-7.13(2H, m), 6.47(2H, brs), 5.00(1H, brs), 4.91(2H, s), 4.16(1H, dd, J = 10.9, 4.4 Hz), 4.03(1H, dd, J = 10.9, 6.4 Hz), 3.76-3.70(1H, m), 3.52(2H, s), 3.39(2H, d, J = 5.6 Hz). Carboxylic acid and one of alcohols were not found.

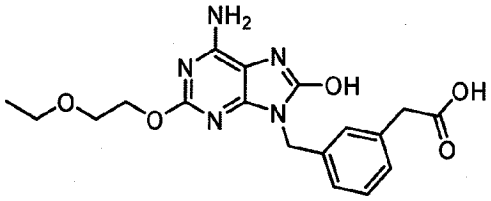
[Example 37]

[0183]

Comparative Example 12: Synthesis of 9-(3-carboxymethylbenzyl)-2-(2-ethoxy-ethoxy)-8-hydroxyadenine

[0184]

[Chemical formula 43]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 89 %

^{1}H NMR(DMSO-d_6)δ 12.31(1H, brs), 9.97(1H, s), 7.26(1H, dd, J = 7.6, 7.5 Hz), 7.20(1H, s), 7.16-7.14(2H, m), 6.47(2H, brs), 4.83(2H, s), 4.25(2H, t, J = 4.8 Hz), 3.63(2H, t, J = 4.8 Hz), 3.53(2H, s), 3.45(2H, q, J = 7.0 Hz), 1.10(3H, t, J = 7.0 Hz).

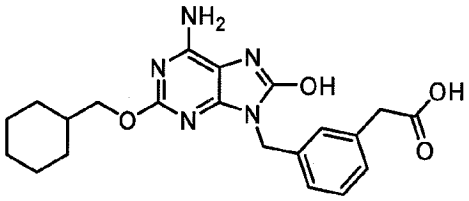
[Example 38]

[0185]

Comparative Example 13: Synthesis of 9-(3-carboxymethylbenzyl)-2-cyclohexyl-methoxy-8-hydroxyadenine

[0186]

[Chemical formula 44]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 90 %

^{1}H NMR(DMSO-d_6)δ 10.27(1H, brs), 7.23(1H, dd, J = 7.5, 7.5 Hz), 7.19-7.10(3H, m), 6.56(2H, brs), 4.81(2H, s), 3.94(2H, d, J = 6.2 Hz), 3.48(2H, s), 1.74-1.61(6H, m), 1.23-1.14(3H, m), 1.02-0.94(2H, m).

Carboxylic acid was not found.

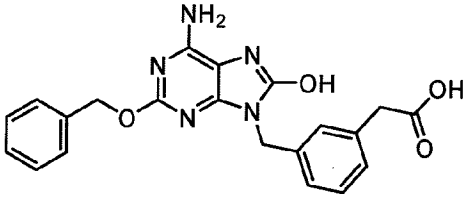
[Example 39]

[0187]

Comparative Example 14: Synthesis of 2-benzyloxy-9-(3-carboxymethylbenzyl)-8-hydroxyadenine

[0188]

[Chemical formula 45]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 100 %

^{1}H NMR(DMSO-d_6)δ 12.40(1H, brs), 10.29(1H, brs), 7.42-7.40(2H, m), 7.36-

7.20(5H, m), 7.15-7.11(2H, m), 6.61(2H, brs), 5.24(2H, s), 4.83(2H, s), 3.49(2H, s).

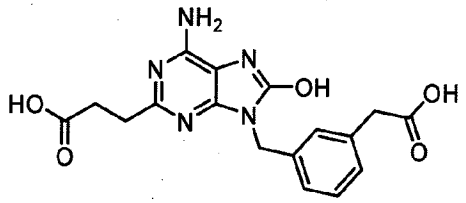
[Example 40]

[0189]

Comparative Example 15: Synthesis of 2-(2-carboxyethyl)-9-(3-carboxymethyl-benzyl)-8-hydroxyadenine

[0190]

[Chemical formula 46]



The titled compound was prepared in the same method as in Comparative Example 1. Yield: 79 %

^{1}H NMR(DMSO-d_6)δ 12.50(2H, brs), 10.10(1H, s), 7.25(1H, dd, J = 7.6, 7.4 Hz), 7.25(1H, s), 7.18(1H, d, 7.6 Hz), 7.16(1H, d, 7.4 Hz), 6.29(2H, brs), 4.86(2H, s), 3.52(2H, s), 2.83(2H, t, J = 7.2 Hz), 2.64(2H, t, J = 7.2 Hz).

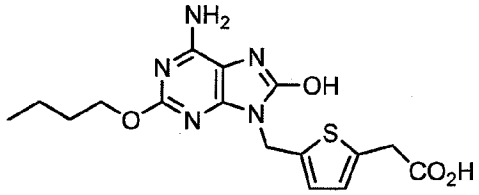
[Example 41]

[0191]

Comparative Example 16: Synthesis of 2-butoxy-9-{(5-carboxylmethyl-2-thienyl)methyl}-8-hydroxyadenine

[0192]

[Chemical formula 47]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 96 %

^{1}H NMR(DMSO-d_6)δ 12.47(1H, brs), 9.94(1H, s), 6.89(1H, d, J = 3.4 Hz), 6.75(1H, d, J = 3.5 Hz), 6.45(2H, brs), 4.94(2H, s), 4.17(2H, t, J = 6.6 Hz), 3.72(2H, s), 1.65(2H, 5, J = 6.6 Hz), 1.38(2H, 6, J = 7.5 Hz), 0.92(3H, t, J = 7.3Hz).

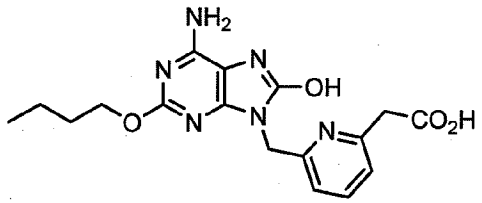
[Example 42]

[0193]

Comparative Example 18: Synthesis of 2-butoxy-9-{(6-carboxylmethyl-2-pyridyl)methyl}-8-hydroxyadenine

[0194]

[Chemical formula 48]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 68 %

^{1}H NMR(DMSO-d_6)δ 12.39(1H, brs), 9.96(1H, brs), 7.62(1H, t, J = 7.7 Hz), 7.17(1H, d, J = 7.6 Hz), 6.85(1H, d, J = 7.7 Hz), 6.43(2H, brs), 4.85(2H, s), 4.01(2H, t, J = 6.6 Hz), 3.651(2H, s), 1.51(2H, 5, J = 6.6 Hz), 1.26(2H, 6, J = 7.3 Hz), 0.80(3H, t, J = 7.3 Hz).

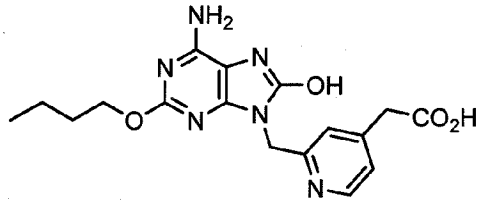
[Example 43]

[0195]

Comparative Example 19: Synthesis of 2-butoxy-9-{(4-carboxylmethyl-2-pyridyl)-methyl}-8-hydroxyadenine

[0196]

[Chemical formula 49]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 58 %

^{1}H NMR(DMSO-d_6)δ 10.77(1H, brs), 8.28(1H, d, J = 5.0 Hz), 7.13(1H, d, J = 4.9 Hz), 7.04(1H, s), 6.69(2H, brs), 4.91(2H, s), 4.07(2H, t, J = 6.6 Hz), 3.28(2H, s), 1.57(2H, 5, J = 6.6 Hz), 1.33(2H, 6, J = 7.4 Hz), 0.87(3H, t, J = 7.3 Hz).

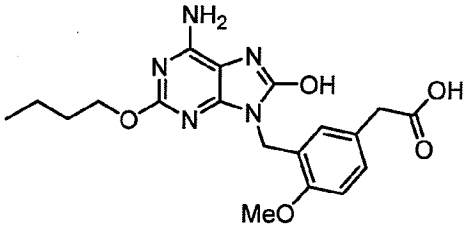
[Example 44]

[0197]

Comparative Example 20: Synthesis of 2-butoxy-9-(5-carboxymethyl-2-methoxy)-benzyl-8-hydroxyadenine

[0198]

[Chemical formula 50]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 88 %

^{1}H NMR(DMSO-d_6)δ 12.25(1H, brs), 10.17(1H, brs), 7.12(1H, d, J = 8.4 Hz),

6.96(1H, d, J = 8.4 Hz), 6.68(1H, s), 6.51(2H, brs), 4.80(2H, s), 4.08(2H, t, J = 6.6 Hz), 3.82(3H, s), 3.36(2H, s), 1.58(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.33(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.87(3H, t, J = 7.4 Hz).

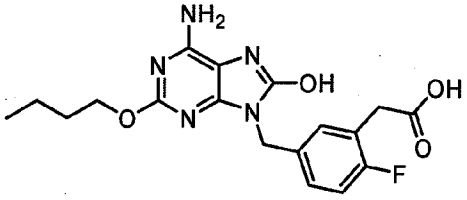
[Example 45]

[0199]

Comparative Example 21: Synthesis of 2-butoxy-9-(3-carboxymethyl-4-fluoro)-benzyl-8-hydroxyadenine

[0200]

[Chemical formula 51]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 92 %

^{1}H NMR(DMSO-d_6)δ 12.51(1H, brs), 10.12(1H, s), 7.27(1H, dd, J = 7.2, 2.1 Hz), 7.22(1H, m), 7.11(1H, dd, J = 9.7, 8.5 Hz), 6.50(2H, brs), 4.81(2H, s), 4.14(2H, t, J = 6.6 Hz), 3.56(2H, s), 1.63(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.37(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.90(3H, t, J = 7.4 Hz).

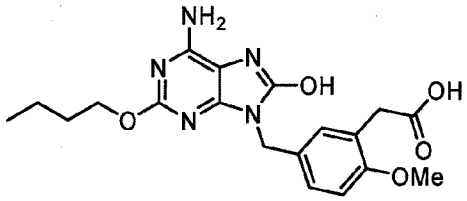
[Example 46]

[0201]

Comparative Example 22: Synthesis of 2-butoxy-9-(3-carboxymethyl-4-methoxy)-benzyl-8-hydroxyadenine

[0202]

[Chemical formula 52]



The titled compound was prepared in the same method as in Comparative Example 1 as a white solid. Yield: 89 %

^{1}H NMR(DMSO-d_6)δ 12.12(1H, brs), 9.95(1H, s), 7.18(1H, d, J = 8.2 Hz), 7.14(1H, s), 6.90(2H, d, J = 8.4), 6.44(2H, brs), 4.75(2H, s), 4.14(2H, t, J = 6.6 Hz), 3.71(3H, s), 3.43(2H, s), 1.62(2H, 5, J = 7.0 Hz), 1.37(2H, 6, J = 7.5 Hz), 0.90(3H, t, J = 7.4 Hz).

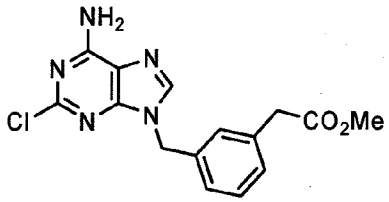
[Example 47]

[0203]

Reference Example 1: Synthesis of 2-chloro-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0204]

[Chemical formula 53]



2-Chloroadenine (1.70 g, 10.0 mmol) and potassium carbonate (9.67 g, 70.0 mmol) were added to DMF (35 ml), and the solution was stirred at 60°C for 1.5 hours. After being cooled, methyl 3-bromomethylphenylacetate (3.16 g, 13.0 mmol) was added thereto and the mixture was stirred at room temperature for 1.5 hours. After removal of the solvent by evaporation, thereto was added chloroform (50 ml) and the precipitated solid was taken by filtration and washed with water to give the titled compound as a pale yellow solid (2.13 g, 6.41 mmol). Yield: 64 %

^{1}H NMR(DMSO-d_6)δ 8.24(1H, s), 7.80(2H, brs), 7.31(1H, dd, J = 7.6, 7.6 Hz), 7.19(1H, d, 7.6 Hz), 7.18(1H, s), 7.14(1H, d, 7.6 Hz), 5.32(2H, s), 3.66(2H, s), 3.59(3H, s).

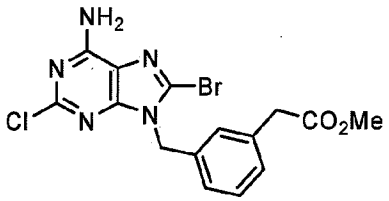
[Example 48]

[0205]

Reference Example 2: Synthesis of 8-bromo-2-chloro-9-(3-methoxycarbonyl-methylbenzyl)adenine

[0206]

[Chemical formula 54]



2-Chloro-9-(3-methoxycarbonylmethylbenzyl)adenine (2.00 g, 6.03 mmol) prepared in Reference Example 1 and sodium acetate (2.95 g, 36.0 mmol) were added to chloroform (100 ml) and thereto was added dropwise bromine (4.79 g, 30.0 mmol), and the mixture was stirred at room temperature for 5 hours. To the reaction mixture was added water, and the mixture was extracted with chloroform. The organic layer was washed successively with a saturated aqueous sodium bicarbonate solution, a saturated aqueous sodium hydrogen sulfite solution and saturated brine in this order, dried over anhydrous magnesium sulfate and concentrated to give the titled compound as a brown solid (1.78 g, 4.34 mmol). Yield: 72 %

^{1}H NMR($CDCl_3$)δ 7.32(1H, dd, J = 8.0, 7.6 Hz), 7.26-7.19(3H, m), 5.72(2H, brs), 5.34(2H, s), 3.70(3H, s), 3.61(2H, s).

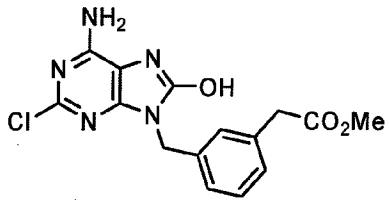
[Example 49]

[0207]

Reference Example 3: Synthesis of 2-chloro-8-hydroxy-9-(3-methoxycarbonyl-methylbenzyl)adenine

[0208]

[Chemical formula 55]



8-Bromo-2-chloro-9-(3-methoxycarbonylmethylbenzyl)adenine (1.78 g, 4.34 mmol) prepared in Reference Example 2 was suspended in a mixture of 1N aqueous sodium hydroxide solution (150 ml) and methanol (150 ml), and the suspension was stirred at 100°C for 30 minutes. After neutralizing with 12N hydrochloric acid, the solvent was removed by evaporation, and to the residue were added methanol (50 ml) and conc. sulfuric acid (2.45 g, 25.0 mmol), and the mixture was refluxed for 1 hour. After neutralizing with a saturated aqueous sodium bicarbonate solution, the solution was extracted with chloroform and the organic layer was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (SiO_2 90.0g, elute: $CHCl_3$/MeOH=100/0~50/1) to give the titled compound as a white solid (0.84 g, 2.41 mmol). Yield: 56 %

^{1}H NMR(DMSO-d_6)δ 10.37(1H, brs), 7.29(1H, dd, J = 8.0, 4.8 Hz), 7.18-7.12(3H, m), 6.91(2H, brs), 4.88(2H, s), 3.65(2H, s), 3.58(3H, s).

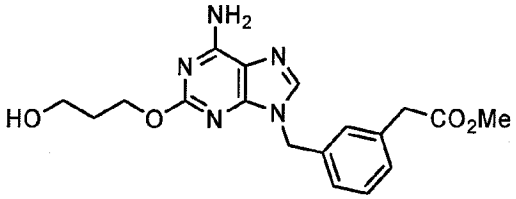
[Example 50]

[0209]

Reference Example 4: Synthesis of 2-(3-hydroxypropoxy)-9-(3-methoxycarbonyl-methylbenzyl)adenine

[0210]

[Chemical formula 56]



After sodium (0.43 g, 18.70 mmol) was dissolved in 1,3-dipropanol (15 ml), thereto was added 2-chloro-9-(3-methoxycarbonylmethylbenzyl)adenine (0.53 g, 1.60 mmol) prepared in Reference Example 1 and the mixture was stirred at 100°C for 5 hours. After neutralizing with 12N hydrochloric acid, the solvent was removed by evaporation, and to the residue were added methanol (100ml) and conc. sulfuric acid (5 ml), and the mixture was refluxed for 5 hours. After neutralizing with a saturated aqueous sodium bicarbonate solution, the solution was extracted with chloroform, dried over anhydrous magnesium sulfate

and concentrated. The residue was purified by column chromatography (SiO_2 20 g, elute: $CHCl_3$/MeOH=100/0~30/1) to give the titled compound as a pale yellow solid (0.39 g, 1.05 mmol). Yield: 66 %

^{1}H NMR(DMSO-d_6)δ8.02(1H, s), 7.29(1H, t, J = 7.6 Hz), 7.20(5H, m), 5.24(2H, s), 4.51(1H, t, J = 5.2 Hz), 4.26(2H, t, J = 6.5 Hz), 3.65(2H, s), 3.58(3H, s), 3.52(2H, q, J = 5.2 Hz), 1.82(2H, qui, J = 6.4 Hz).

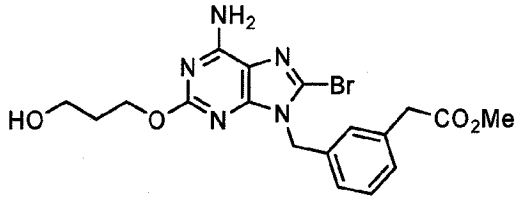
[Example 51]

[0211]

Reference Example 5: Synthesis of 8-bromo-2-(3-hydroxypropoxy)-9-(3-methoxycarbonylmethylbenzyl)adenine

[0212]

[Chemical formula 57]



The titled compound was prepared in the same method as in Reference Example 2 as a brown solid. Yield: 94 %

^{1}H NMR(DMSO-d_6)δ7.43(2H, brs), 7.29(1H, t, J = 7.6 Hz), 7.19(1H, d, J = 7.6 Hz), 7.18(1H, s), 7.09(1H, d, J = 7.8 Hz), 5.34(2H, s), 4.51(1H, t, J = 5.1 Hz), 4.26(2H, t, J = 6.5 Hz), 3.65(2H, s), 3.58(3H, s), 3.52(2H, q, J = 5.3 Hz), 1.81(2H, qui, J = 6.4 Hz).

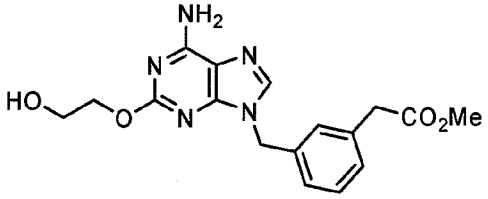
[Example 52]

[0213]

Reference Example 6: Synthesis of 2-(2-hydroxyethoxy)-9-(3-methoxycarbonylmethylbenzyl)adenine

[0214]

[Chemical formula 58]



The titled compound was prepared in the same method as in Reference Example 4 as a white solid. Yield: 94 %

^{1}H NMR(DMSO-d_6)δ8.22(1H, s), 7.65(2H, s), 7.30(1H, t, J = 7.6 Hz), 7.26(1H, s), 7.20(2H, m), 5.28(2H, s), 4.29(2H, t, J = 5.0 Hz), 3.69(2H, t, J = 5.3 Hz), 3.66(2H, s), 3.61(3H, s).

[Example 53]

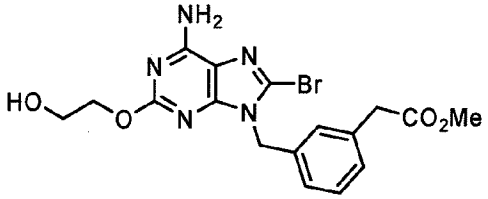
[0215]

Reference Example 7: Synthesis of 8-bromo-2-(2-hydroxyethoxy)-9-(3-methoxy-

carbonylmethylbenzyl)adenine

[0216]

[Chemical formula 59]



The titled compound was prepared in the same method as in Reference Example 2 as a white solid. Yield: 63 %

^{1}H NMR(DMSO-d_6)δ7.44(2H, brs), 7.30(1H, t, J = 7.6 Hz), 7.19(1H, t, J = 7.6 Hz), 7.18(1H, s), 7.11(1H, t, J = 7.7 Hz), 5.23(2H, s), 4.81(1H, t, J = 5.6 Hz), 4.22(2H, t, J = 5.4 Hz), 3.67(4H, m), 3.58(3H, s).

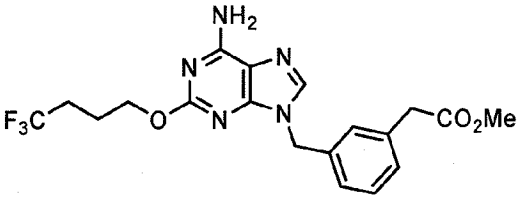
[Example 54]

[0217]

Reference Example 8: Synthesis of 9-(3-methoxycarbonylmethylbenzyl)-2-(4,4,4-trifluorobutoxy)adenine

[0218]

[Chemical formula 60]



The titled compound was prepared in the same method as in Reference Example 4 as a yellow solid. Yield: 73 %

^{1}H NMR(DMSO-d_6)δ8.04(1H, s), 7.24(6H, m), 5.24(2H, s), 4.27(2H, t, J = 6.3 Hz), 3.65(2H, s), 3.58(3H, s), 2.37(2H, m), 1.91(2H, m).

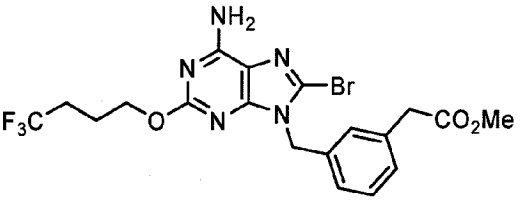
[Example 55]

[0219]

Reference Example 9: Synthesis of 8-bromo-9-(3-methoxycarbonylmethylbenzyl)-2-(4,4,4-trifluorobutoxy)adenine

[0220]

[Chemical formula 61]



The titled compound was prepared in the same method as in Reference Example 2 as a white solid. Yield: 94 %

^{1}H NMR(DMSO-d_6)δ7.50(2H, brs), 7.30(1H, t, J = 7.9 Hz), 7.19(1H, d, J = 7.6 Hz),

7.18(1H, s), 7.10(1H, d, J = 7.7 Hz), 5.24(2H, s), 4.27(2H, t, J = 6.3 Hz), 3.65(2H, s), 3.58(3H, s), 2.37(2H, m), 1.91(2H, m).

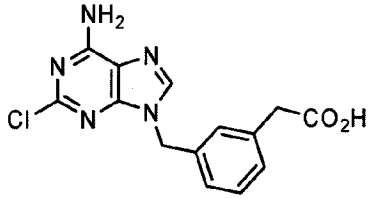
[Example 56]

[0221]

Reference Example 10: Synthesis of 9-(3-carboxymethylbenzyl)-2-chroloadenine

[0222]

[Chemical formula 62]



2-Chloro-9-(3-methoxycarbonylmethylbenzyl)adenine (600 mg, 1.81 mmol) prepared in Reference Example 1 was dissolved in a mixture of 1N aqueous sodium hydroxide solution (18 ml) and methanol (8 ml), and the solution was stirred at room temperature for 6 hours. After neutralizing with 12N hydrochloric acid, the solvent was removed by evaporation, and to the residue was added water. The precipitated solid was taken by filtration to give the titled compound as a white solid (560 mg, 1.76 mmol). Yield: 97 %

^{1}H NMR(DMSO-d_6)δ8.24(1H, s), 7.79(2H, brs), 7.19(4H, m), 5.31(2H, s), 3.53(2H, s).

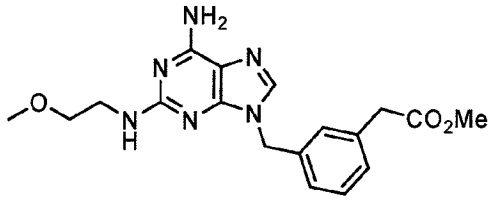
[Example 57]

[0223]

Reference Example 11: Synthesis of 9-(3-methoxycarbonylmethylbenzyl)-2-(N-2-methoxyethylamino)adenine

[0224]

[Chemical formula 63]



9-(3-Carboxymethylbenzyl)-2-chloroadenine (0.100 g, 0.32 mmol) prepared in Reference Example 10 was added to 2-methoxyethylamine (3 ml, 34.5 mmol), and the mixture was stirred at 150°C for 4 hours in an autoclave. After removal of the solvent by evaporation, thereto were added methanol (1 ml) and conc. sulfuric acid (0.2 ml), and the mixture was refluxed for 2 hours. After neutralizing with a saturated aqueous sodium bicarbonate solution, the solution was extracted with chloroform, dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (SiO_2 7.0 g, elute: $CHCl_3$/MeOH=100/0~50/1) to give the titled compound as a brown oil (69 mg, 0.19 mmol). Yield: 59 %

^{1}H NMR(DMSO-d_6)δ7.79(1H, s), 7.28(1H, t, J = 7.6 Hz), 7.22(1H, s), 7.28(2H, m), 6.69(2H, brs), 6.16(1H, brm), 5.16(2H, s), 3.64(2H, s), 3.52(4H, m), 3.23(3H, s).

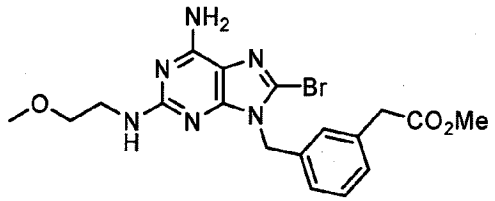
[Example 58]

[0225]

Reference Example 12: Synthesis of 8-bromo-9-(3-methoxycarbonylmethyl-benzyl)-2-(N-2-methoxyethylamino)adenine

[0226]

[Chemical formula 64]



The titled compound was prepared in the same method as in Reference Example 2 as a brown solid. Yield: 88 %

^{1}H NMR(DMSO-d_6)δ7.29(1H, t, J = 7.6 Hz), 7.18(3H, m), 6.91(2H, brs), 6.36(1H, brm), 5.16(2H, s), 3.65(2H, s), 3.58(3H, s), 3.41(4H, m), 3.23(3H, s).

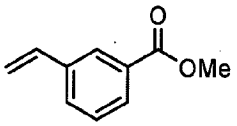
[Example 59]

[0227]

Reference Example 13: Synthesis of methyl 3-vinylbenzoate

[0228]

[Chemical formula 65]



To a solution of 3-vinylbenzoic acid (3.0 g, 20 mmol) in DMF (15 ml) were added methyl iodide (3.7 ml, 60 mmol) and potassium carbonate (4.1 g, 30 mmol), and the solution was stirred at room temperature for 2 hours. After confirming disappearance of the starting material by TLC, to the solution was added water and the solution was extracted with ethyl acetate (30 ml×3). The organic layer was concentrated to give the titled compound as a colorless liquid (3.0 g, 18.6 mmol). Yield: 92 %

^{1}H NMR($CDCl_3$)δ 8.08(1H, s), 7.93(1H, d, J = 7.7 Hz), 7.59(1H, d, J = 7.7 Hz), 7.39(1H, dd, J = 7.7, 7.7 Hz), 6.75(1H, dd, J = 17.6, 10.9 Hz), 5.83(1H, d, J = 17.6 Hz), 5.32(1H, d, J = 10.9 Hz), 3.93(3H, s).

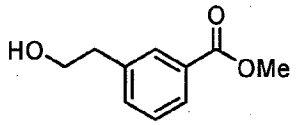
[Example 60]

[0229]

Reference Example 14: Synthesis of methyl 3-(2-hydroxyethyl)benzoate

[0230]

[Chemical formula 66]



To methyl 3-vinylbenzoate (3.0 g, 18.6 mmol) prepared in Reference Example 13 was added dropwise 9-BBN (0.5 M THF solution) (50 ml, 25 mmol), and the mixture was stirred at room temperature for 15 hours. Then, to the mixture were added at 0°C water (14 ml) and 30 % aqueous hydrogen peroxide solution (14 ml), and the mixture was stirred at room temperature for 2 hours. After addition of 2N aqueous sodium hydroxide solution (3.75 ml), the mixture was stirred for 2 hours. Then the reaction was quenched by adding at 0°C a saturated aqueous sodium thiosulfate solution, and the reaction mixture was extracted with ethyl acetate (30 ml×3). The organic layer was concentrated and the residue was purified by column chromatography (SiO_2 110 g, elute: Hex/AcOEt = 2/1) to give the titled compound as a colorless liquid (2.8 g, 15.4 mmol). Yield: 83 %

^{1}H NMR($CDCl_3$)δ 7.92(1H, s), 7.91(1H, d, J = 6.6 Hz), 7.46-7.37(2H, m), 3.93(3H, s), 3.90(2H, t, J = 6.5 Hz), 2.93(2H, t, J = 6.5 Hz), 1.50(1H, brs).

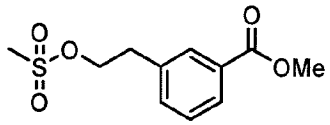
[Example 61]

[0231]

:Synthesis of methyl 3-(2-methanesulfonyloxyethyl)benzoate

[0232]

[Chemical formula 67]



To a solution of methyl 3-(2-hydroxyethyl)benzoate (2.8 g, 15.4 mmol) prepared in Reference Example 14 in THF (30 ml) were added at 0°C methanesulfonyl chloride (1.4 ml, 18.5 mmol) and triethylamine (2.6 ml, 18.5 mmol), and the solution was stirred at room temperature for 30 minutes. Thereto was added water and the mixture was extracted with ethyl acetate (30 ml×3). The organic layer was concentrated and the residue was purified by column chromatography (SiO_2 90 g, elute: Hex/AcOEt=3/1) to give the titled compound as a colorless liquid (3.4 g, 13.1 mmol). Yield: 85 %

^{1}H NMR($CDCl_3$)δ 7.96-7.94(1H, m), 7.92(1H, s), 7.45-7.41(2H, m), 4.44(2H, t, J = 6.8 Hz), 3.93(3H, s), 3.12(2H, t, J = 6.8 Hz), 2.89(3H, s).

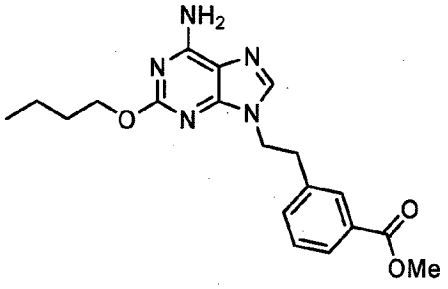
[Example 62]

[0233]

Reference Example 16: Synthesis of 2-butoxy-9-[2-(3-methoxycarbonylphenyl)-ethyl]adenine

[0234]

[Chemical formula 68]



The titled compound was prepared in the same method as in Reference Example 1 as a white solid. Yield: 81 %

^{1}H NMR($CDCl_3$)δ 7.91(1H, d, J = 7.7 Hz), 7.85(1H, s), 7.33(1H, dd, J = 7.7, 7.6 Hz), 7.28(1H, s), 7.20(1H, d, J = 7.6 Hz), 5.59(2H, brs), 4.37(2H, t, J = 7.0 Hz), 4.33(2H, t, J = 6.6 Hz), 3.92(3H, s), 3.22(2H, t, J = 7.0 Hz), 1.80(2H, tt, J = 7.4 Hz, 6.6 Hz), 1.52(2H, tq, J = 7.4 Hz, 7.4 Hz), 0.99(3H, t, J = 7.4 Hz).

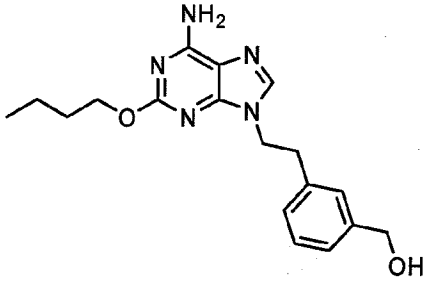
[Example 63]

[0235]

Reference Example 17: Synthesis of 2-butoxy-9-[2-(3-hydroxymethylphenyl)-ethyl]adenine

[0236]

[Chemical formula 69]



Aluminum lithium hydride (65 mg, 1.71 mmol) was added to THF (10 ml), and thereto was added dropwise on an ice bath a solution of 2-butoxy-9-[2-(3-methoxycarbonylphenyl)ethyl]adenine (0.40 g, 1.08 mmol) prepared in Reference Example 16 in THF (20 ml), and the mixture was stirred at room temperature for 2 hours. To the mixture were successively added dropwise water (0.07 ml), 1N aqueous sodium hydroxide solution (0.3 ml), and water (0.3 ml) on an ice bath in this order. After filtration over celite, the filtrate was concentrated and the resulting crude crystals were recrystallized from chloroform/hexane to give the titled compound as a white solid (0.25 g, 0.74 mmol). Yield: 68 %

^{1}H NMR($CDCl_3$)δ 7.27-7.22(3H, m), 7.03(1H, s), 7.03-7.01(1H, m), 5.56(2H, brs), 4.64(2H, s), 4.34(2H, t, J = 6.9 Hz), 4.34(2H, t, J = 6.6 Hz), 3.15(2H, t, J = 6.9 Hz), 1.84-1.77(2H, m), 1.53(2H, tq, J = 7.4 Hz, 7.4 Hz), 0.99(3H, t, J = 7.4 Hz).

[Example 64]

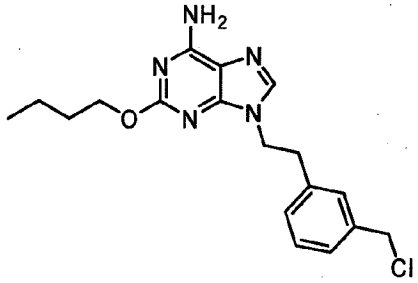
[0237]

Reference Example 18: Synthesis of 2-butoxy-9-[2-(3-chloromethylphenyl)-

ethyl]adenine

[0238]

[Chemical formula 70]



To a solution of 2-butoxy-9-[2-(3-hydroxymethylphenyl)ethyl]adenine (0.25 g, 0.72 mmol) prepared in Reference Example 17 in chloroform (7.5 ml) was added thionyl chloride (0.26 ml, 3.6 mmol), and the mixture was refluxed for 1.5 hours. After allowed to cool, the solution was neutralized with a 5 % aqueous sodium bicarbonate solution, and extracted with chloroform (30 ml×3). The organic layer was concentrated to give the titled compound as a pale yellow liquid (0.25 g, 0.70 mmol). Yield: 97 %

^{1}H NMR($CDCl_3$)δ 7.28-7.23(3H, m), 7.12(1H, s), 7.03-7.00(1H, m), 5.76(2H, brs), 4.53(2H, s), 4.34(2H, t, J = 7.0 Hz), 4.34(2H, t, J = 6.6 Hz), 3.16(2H, t, J = 7.0 Hz), 1.80(2H, tt, J = 7.4 Hz, 6.6 Hz), 1.52(2H, tq, J = 7.4 Hz, 7.4 Hz), 0.99(3H, t, J = 7.4 Hz).

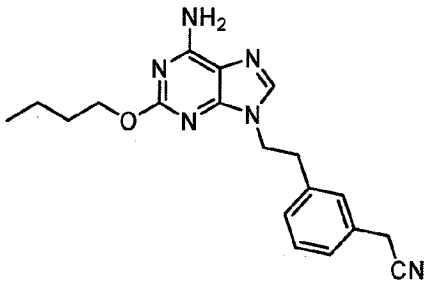
[Example 65]

[0239]

Reference Example 19: Synthesis of 2-butoxy-9-[2-(3-cyanomethylphenyl)-ethyl]adenine

[0240]

[Chemical formula 71]



To a solution of 2-butoxy-9-[2-(3-chloromethylphenyl)ethyl]adenine (0.25 g, 0.70 mmol) prepared in Reference Example 18 in DMF (7 ml) was added sodium cyanide (0.10 g, 2.1 mmol), and the mixture was stirred at room temperature for 6 hours. After neutralizing with 1N hydrochloric acid (1.4 ml), the solution was concentrated by an evaporator to remove DMF. The residue was extracted with chloroform (30 ml×3), and the extract was concentrated. The obtained crude crystals were recrystallized from chloroform/hexane to give the titled compound as a white solid (0.20 g, 0.59 mmol). Yield: 84 %

^{1}H NMR($CDCl_3$)δ 7.52-7.26(2H, m), 7.19(1H, d, J = 8.2 Hz), 7.05-6.99(2H, m), 5.50(2H, brs), 4.34(2H, t, J = 7.0 Hz), 4.34(2H, t, J = 6.6 Hz), 3.70(2H, s), 3.17(2H, t, J = 7.0 Hz), 1.84-1.76(2H, m), 1.57-1.47(2H, m), 0.99(3H, t, J = 7.4 Hz).

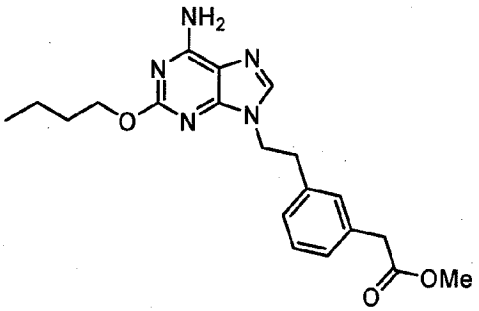
[Example 66]

[0241]

Reference Example 20: Synthesis of 2-butoxy-9-[2-(3-methoxycarbonylmethyl-phenyl)ethyl]adenine

[0242]

[Chemical formula 72]



To 2-butoxy-9-[2-(3-cyanomethylphenyl)ethyl]adenine (0.20 g, 0.57 mmol) prepared in Reference Example 19 were added methanol (6 ml) and 5N aqueous sodium hydroxide solution (6 ml), and the solution was refluxed for 3 hours. After neutralizing with conc. hydrochloric acid at 0°C, the precipitated white solid was taken by filtration, washed with water and dried in vacuo for 12 hours. Then, thereto were added methanol (6 ml) and conc. sulfuric acid (0.2 ml), and the solution was refluxed for 1 hour. After neutralizing with a 5 % aqueous sodium bicarbonate solution, the precipitated solid was taken by filtration and washed with water to give the titled compound as a white solid (0.18 g, 0.46 mmol). Yield: 81 %

^{1}H NMR($CDCl_3$)δ 7.29(1H, s), 7.24(1H, dd, J = 7.6, 7.6 Hz), 7.15(1H, d, J = 7.6 Hz), 7.03(1H, s), 6.97(1H, d, J = 7.6 Hz), 5.79(2H, brs), 4.34(2H, t, J = 6.7 Hz), 4.34(2H, t, J = 6.7 Hz), 3.69(3H, s), 3.58(2H, s), 3.14(2H, t, J = 7.0 Hz), 1.80(2H, tt, J = 7.5 Hz, 6.7 Hz), 1.52(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.99(3H, t, J = 7.4 Hz).

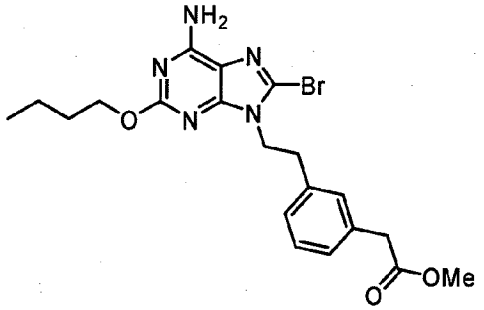
[Example 67]

[0243]

Reference Example 21: Synthesis of 8-bromo-2-butoxy-9-[2-(3-methoxy-carbonylmethylphenyl)ethyl]adenine

[0244]

[Chemical formula 73]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 88%

^{1}H NMR($CDCl_3$)δ 7.25(1H, dd, J = 7.7, 7.6 Hz), 7.15(1H, d, J = 7.7 Hz), 7.07(1H, s), 7.05(1H, d, J = 7.6 Hz), 5.57(2H, brs), 4.33(2H, t, J = 7.5 Hz), 4.31(2H, t, J = 6.6 Hz), 3.70(3H, s), 3.59(2H, s), 3.10(2H, t, J = 7.5 Hz), 1.79(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.52(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.99(3H, t, J = 7.4 Hz).

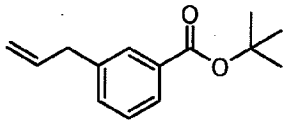
[Example 68]

[0245]

Reference Example 22: Synthesis of tert-butyl 3-allylbenzoate

[0246]

[Chemical formula 74]



To THF (16 ml) was added a solution of isopropylmagnesium bromide (0.76 M THF solution, 26 ml, 20 mmol), and thereto was added dropwise at 0°C butyl lithium (1.59 M hexane solution, 25 ml, 40 mmol). The mixture was stirred for 15 minutes, cooled to -78°C, and further stirred for 20 minutes. Then, thereto was added dropwise a solution of tert-butyl 3-bromobenzoate (2.0 g, 8.0 mmol) in THF (16 ml), and the solution was stirred at -78°C for 30 minutes. Thereto were added allyl bromide (2.8 ml, 32 mmol) and copper cyanide (1 M THF solution, 2.4 ml, 2.4 mmol), and the mixture was stirred for additional 1 hour. The reaction was quenched with a saturated aqueous ammonium chloride solution, and the mixture was extracted with hexane (30 ml×3). The organic layer was concentrated and the residue was purified by column chromatography (SiO_2 60 g, elute: Hex/AcOEt=300/1) to give the titled compound as a colorless liquid (1.0 g, 4.6 mmol). Yield: 58 %

^{1}H NMR($CDCl_3$)δ 7.84-7.82(2H, m), 7.36-7.26(2H, m), 6.00-5.92(1H, m), 5.12-5.06(2H, m), 3.43(2H, d, J = 6.7 Hz), 1.60(9H, s).

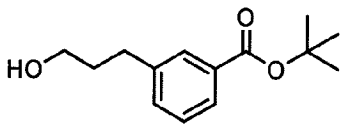
[Example 69]

[0247]

Reference Example 23: Synthesis of tert-butyl 3-(3-hydroxypropyl)benzoate

[0248]

[Chemical formula 75]



The titled compound was prepared in the same method as in Reference Example 14. Yield: 60 %

^{1}H NMR($CDCl_3$)δ 7.83-7.78(2H, m), 7.38-7.31(2H, m), 3.68(2H, t, J = 6.4 Hz), 2.76(2H, t, J = 7.6 Hz), 1.91(2H, tt, J = 7.6 Hz, 6.4 Hz), 1.60(9H, s), 1.30(1H, brs).

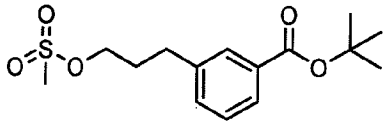
[Example 70]

[0249]

Reference Example 24: Synthesis of tert-butyl 3-(3-methanesulfonyloxypropyl)-benzoate

[0250]

[Chemical formula 76]



The titled compound was prepared in the same method as in Reference Example 15. Yield: 100 %

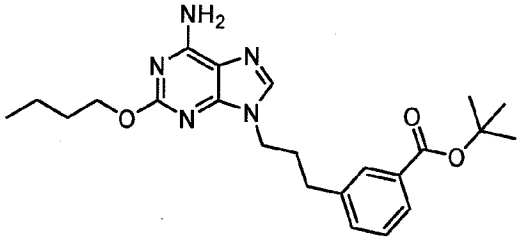
^{1}H NMR($CDCl_3$)δ 7.86-7.82(1H, m), 7.82(1H, s), 7.37-7.35(2H, m), 4.23(2H, t, J = 6.3 Hz), 3.01(3H, s), 2.80(2H, t, J = 7.6 Hz), 2.10(2H, tt, J = 7.6 Hz, 6.3 Hz), 1.60(9H, s).

[Example 71]

[0251]

Reference Example 25: Synthesis of 2-butoxy-9-[3-(3-tert-butoxycarbonylphenyl)-propyl]adenine

[Chemical formula 77]



The titled compound was prepared in the same method as in Reference Example 1. Yield: 72 %

^{1}H NMR($CDCl_3$)δ 7.85-7.82(1H, m), 7.80(1H, s), 7.59(1H, s), 7.34-7.32(2H, m), 5.51(2H, brs), 4.31(2H, t, J = 6.6 Hz), 4.13(2H, t, J = 7.1 Hz), 2.71(2H, t, J = 7.7 Hz), 2.26(2H, tt, J = 7.7 Hz, 7.1 Hz), 1.79(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.60(9H, s), 1.52(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

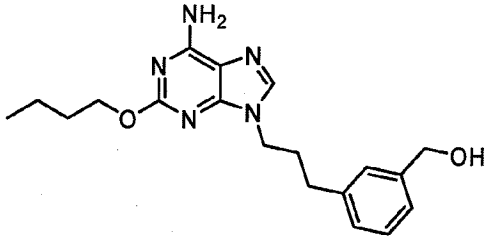
[Example 72]

[0253]

Reference Example 26: Synthesis of 2-butoxy-9-[3-(3-hydroxymethylphenyl)-propyl]adenine

[0254]

[Chemical formula 78]



The titled compound was prepared in the same method as in Reference Example 17. Yield: 97 %

^{1}H NMR($CDCl_3$)δ 7.53(1H, s), 7.25(1H, dd, J = 7.7, 7.5 Hz), 7.17(1H, d, J = 7.7 Hz), 7.14(1H, s), 7.06(1H, d, J = 7.5 Hz), 5.62(2H, brs), 4.66(2H, s), 4.31(2H, t, J = 6.6 Hz), 4.11(2H, t, J = 7.0 Hz), 2.66(2H, t, J = 7.5 Hz), 2.56(1H, brs), 2.24(2H, tt, J = 7.5 Hz, 7.0 Hz), 1.79(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.50(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

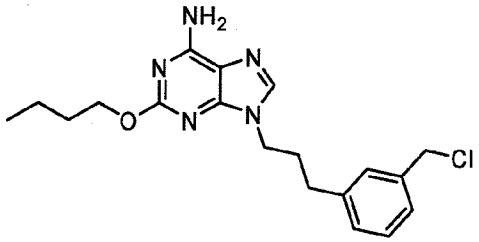
[Example 73]

[0255]

Reference Example 27: Synthesis of 2-butoxy-9-[3-(3-chloromethylphenyl)-propyl]adenine

[0256]

[Chemical formula 79]



The titled compound was prepared in the same method as in Reference Example 18. Yield: 100 %

^{1}H NMR($CDCl_3$)δ 7.59(1H, s), 7.28(1H, dd, J = 7.7, 7.4 Hz), 7.23(1H, d, J = 7.7 Hz), 7.19(1H, s), 7.13(1H, d, J = 7.4 Hz), 5.65(2H, brs), 4.56(2H, s), 4.32(2H, t, J = 6.6 Hz), 4.13(2H, t, J = 7.0 Hz), 2.67(2H, t, J = 7.6 Hz), 2.25(2H, tt, J = 7.6 Hz, 7.0 Hz), 1.79(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.51(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

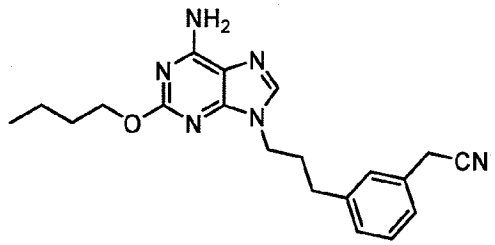
[Example 74]

[0257]

Reference Example 28: Synthesis of 2-butoxy-9-[3-(3-cyanomethylphenyl)propyl]-adenine

[0258]

[Chemical formula 80]



The titled compound was prepared in the same method as in Reference Example 19. Yield: 85 %

^{1}H NMR($CDCl_3$)δ 7.59(1H, s), 7.29(1H, dd, J = 7.5, 7.5 Hz), 7.17-7.11(3H, m), 5.90(2H, brs), 4.32(2H, t, J = 6.6 Hz), 4.13(2H, t, J = 7.0 Hz), 3.72(2H, s), 2.67(2H, t, J = 7.6 Hz), 2.22(2H, tt, J = 7.6 Hz, 7.0 Hz), 1.78(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.52(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

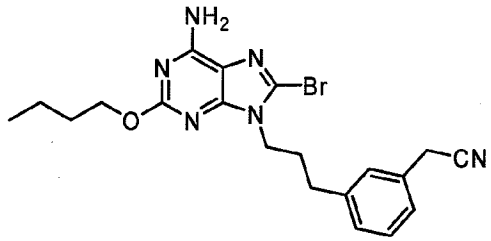
[Example 75]

[0259]

Reference Example 29: Synthesis of 8-bromo-2-butoxy-9-[3-(3-cyanomethyl-phenyl)propyl]adenine

[0260]

[Chemical formula 81]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 85 %

^{1}H NMR($CDCl_3$)δ 7.29-7.25(1H, m), 7.15-7.13(3H, m), 5.41(2H, brs), 4.30(2H, t, J = 6.6 Hz), 4.17(2H, t, J = 7.2 Hz), 3.71(2H, s), 2.71(2H, t, J = 7.7 Hz), 2.19(2H, tt, J = 7.7 Hz, 7.2 Hz), 1.78(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.52(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

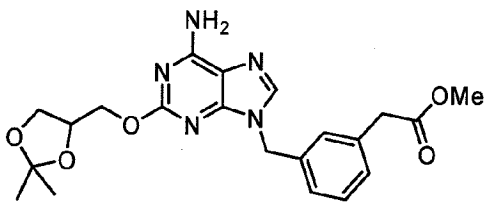
[Example 76]

[0261]

Reference Example 30: Synthesis of 2-(2,2-dimethyl-[1,3]dioxolan-4-ylmethoxy)-9-(3-methoxycarbonylmethylbenzyl)adenine

[0262]

[Chemical formula 82]



After sodium (0.69 g, 30 mmol) was dissolved in 2,2-dimethyl-1,3-dioxolane-4-methanol (30 ml), to the mixture was added 2-chloro-9-(3-methoxycarbonylmethylbenzyl)adenine (1.0 g, 3.0 mmol) prepared in Reference Example 1, and the mixture was stirred at 120°C for 2 hours. After neutralizing with conc. hydrochloric acid at 0°C, the solvent was removed by evaporation. Then, to the residue were added methanol (30 ml) and conc. sulfuric acid (2ml), and the solution was refluxed for 4 hours. After neutralizing with a 5 % aqueous sodium bicarbonate solution, the solvent was removed by evaporation, and to the residue were added acetone (100 ml) and p-toluenesulfonic acid (100 mg). The solution was stirred at room temperature for 48 hours and neutralized with a 5 % aqueous sodium bicarbonate solution. The solvent was removed by evaporation, and the residue was purified by column chromatography (SiO_2 80 g, elute: $CHCl_3$/MeOH = 100/1) to give the titled compound as a pale yellow solid (0.80 g, 1.87 mmol). Yield: 62 %

^{1}H NMR($CDCl_3$)δ 7.61(1H, s), 7.32-7.16(4H, m), 6.06(2H, brs), 5.26(2H, s), 4.52-4.47(2H, m), 4.31-4.26(1H, m), 4.16(1H, dd, J = 8.0, 6.6 Hz), 3.97-3.93(1H, m), 3.68(3H, s), 3.61(2H, s), 1.50(3H, s), 1.37(3H, s).

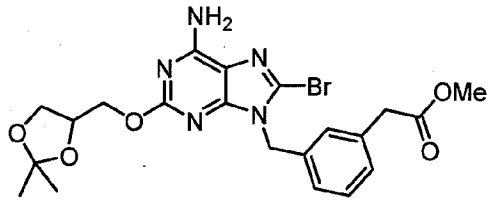
[Example 77]

[0263]

Reference Example 31: Synthesis of 8-bromo-2-(2,2-dimethyl-[1,3]dioxolan-4-yl-methoxy)-9-(3-methoxycarbonylmethylbenzyl)adenine

[0264]

[Chemical formula 83]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 82 %

^{1}H NMR($CDCl_3$)δ 7.30-7.20(4H, m), 6.30(2H, brs), 5.28(2H, s), 4.51-4.28(2H, m), 4.30(1H, dd, J = 10.5, 6.4 Hz), 4.15(1H, dd, J = 8.5, 6.4 Hz), 3.95(1H, dd, J = 8.4, 5.4 Hz), 3.68(3H, s), 3.60(2H, s), 1.48(3H, s), 1.39(3H, s).

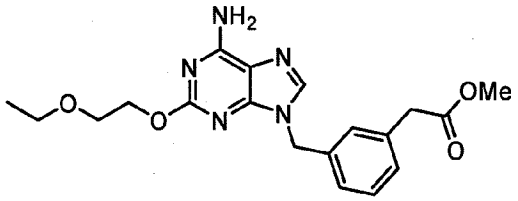
[Example 78]

[0265]

Reference Example 32: Synthesis of 2-(2-ethoxyethoxy)-9-(3-methoxycarbonyl-methylbenzyl)adenine

[0266]

[Chemical formula 84]



The titled compound was prepared in the same method as in Reference Example 4 as a brown solid. Yield: 83 %

^{1}H NMR($CDCl_3$)δ 7.62(1H, s), 7.30(1H, d, J = 7.5 Hz), 7.24-7.16(3H, m), 6.19(2H, brs), 5.26(2H, s), 4.49(2H, t, J = 5.1 Hz), 3.80(2H, t, J = 5.1 Hz), 3.68(3H, s), 3.60(2H, s), 3.59(2H, q, J = 7.0 Hz), 1.23(3H, t, J = 7.0 Hz).

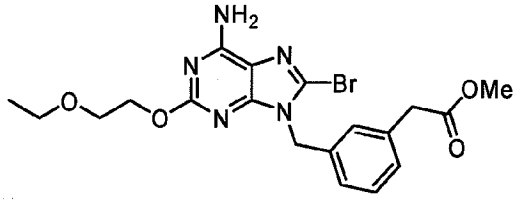
[Example 79]

[0267]

Reference Example 33: Synthesis of 8-bromo-2-(2-ethoxyethoxy)-9-(3-methoxy-carbonylmethylbenzyl)adenine

[0268]

[Chemical formula 85]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 90 %

^{1}H NMR($CDCl_3$)δ 7.29-7.25(2H, m), 7.22-7.20(2H, m), 6.31(2H, brs), 5.28(2H, s), 4.48(2H, t, J = 5.1 Hz), 3.79(2H, t, J = 5.1 Hz), 3.68(3H, s), 3.60(2H, s), 3.59(2H, q, J = 7.0 Hz), 1.24(3H, t, J = 7.0 Hz).

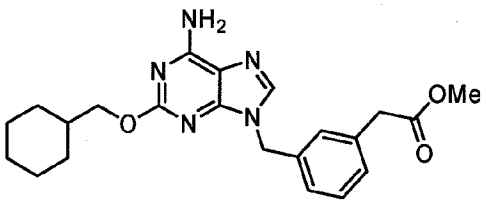
[Example 80]

[0269]

Reference Example 34: Synthesis of 2-cyclohexylmethoxy-9-(3-methoxy-carbonylmethylbenzyl)adenine

[0270]

[Chemical formula 86]



The titled compound was prepared in the same method as in Reference Example 4. Yield: 39

^{1}H NMR($CDCl_3$)δ 7.60(1H, s), 7.31(1H, dd, J = 7.5, 7.5 Hz), 7.24(1H, d, J = 7.5 Hz), 7.23(1H, s), 7.18(1H, d, J = 7.5 Hz), 5.92(2H, brs), 5.26(2H, s), 4.19(2H, d, J = 6.4 Hz), 3.68(3H, s), 3.61(2H, s), 1.90-1.67(6H, m), 1.30-1.23(3H, m), 1.11-

1.05(2H, m).

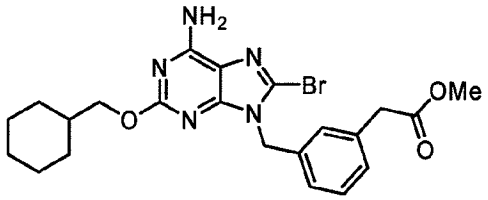
[Example 81]

[0271]

Reference Example 35: Synthesis of 8-bromo-2-cyclohexylmethoxy-9-(3-methoxy-carbonylmethylbenzyl)adenine

[0272]

[Chemical formula 87]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 90 %

^{1}H NMR($CDCl_3$)δ 7.31-7.27(2H, m), 7.24-7.21(2H, m), 5.86(2H, brs), 5.29(2H, s), 4.15(2H, d, J = 6.2 Hz), 3.68(3H, s), 3.60(2H, s), 1.90-1.67(6H, m), 1.30-1.23(3H, m), 1.11-1.04(2H, m).

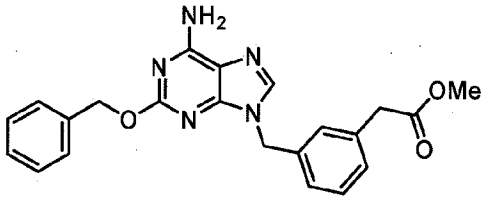
[Example 82]

[0273]

Reference Example 36: Synthesis of 2-benzyloxy-9-(3-methoxycarbonylmethyl-benzyl)adenine

[0274]

[Chemical formula 88]



The titled compound was prepared in the same method as in Reference Example 4. Yield: 72 %

^{1}H NMR($CDCl_3$)δ 7.62(1H, s), 7.49-7.46(2H, m), 7.35-7.16(7H, m), 5.98(2H, brs), 5.43(2H, s), 5.26(2H, s), 3.68(3H, s), 3.60(2H, s).

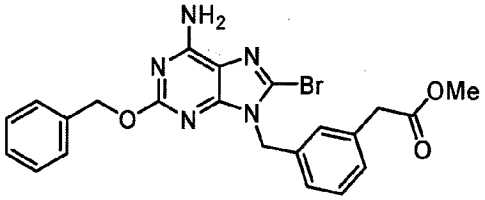
[Example 83]

[0275]

Reference Example 37: Synthesis of 2-benzyloxy-8-bromo-9-(3-methoxycarbonyl-methylbenzyl)adenine)

[0276]

[Chemical formula 89]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 89 %

^{1}H NMR($CDCl_3$)δ 7.47-7.45(2H, m), 7.36-7.17(7H, m), 5.91(2H, brs), 5.42(2H, s), 5.28(2H, s), 3.66(3H, s), 3.58(2H, s).

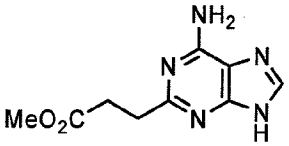
[Example 84]

[0277]

Reference Example 38: Synthesis of 2-(2-methoxycarbonylethyl)adenine

[0278]

[Chemical formula 90]



9-Benzyl-2-(2-methoxycarbonylethyl)adenine (0.29 g, 0.93 mmol) and 20 % $Pd(OH)_2/C$ (0.32 g) were added to a mixture of isopropanol (8 ml) and formic acid (8 ml), and the mixture was stirred under 2 atm of hydrogen atmosphere at 70°C for 40 hours. After filtration, the filtrate was concentrated to give the titled compound as a white solid (0.23 g, 0.86 mmol).

^{1}H NMR(DMSO-d_6)δ 12.70(1H, brs), 8.01(1H, s), 7.00(2H, brs), 3.58(3H, s), 2.91(2H, t, J = 7.1 Hz), 2.76(2H, t, J = 7.1 Hz).

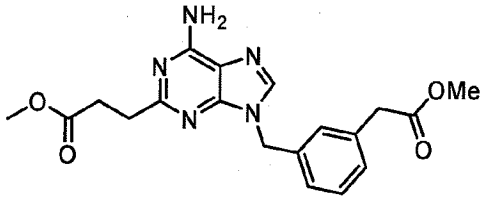
[Example 85]

[0279]

Reference Example 39: Synthesis of 2-(2-methoxycarbonylethyl)-9-(3-methoxycarbonylmethylbenzyl)adenine

[0280]

[Chemical formula 91]



The titled compound was prepared in the same method as in Reference Example 1. Yield: 77 %

^{1}H NMR($CDCl_3$)δ 7.71(1H, s), 7.31(1H, dd, J = 7.9, 7.7 Hz), 7.24-7.22(2H, m), 7.18(1H, d, J = 7.7 Hz), 5.94(2H, brs), 5.30(2H, s), 3.69(3H, s), 3.66(3H, s), 3.62(2H, s), 3.18(2H, t, J = 7.2 Hz), 2.88(2H, t, J = 7.2 Hz).

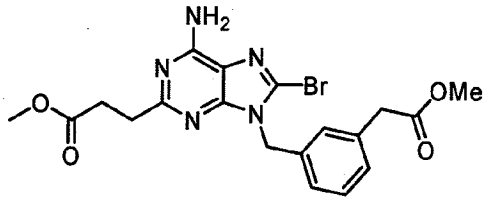
[Example 86]

[0281]

Reference Example 40: Synthesis of 8-bromo-2-(2-methoxycarbonylethyl)-9-(3-methoxycarbonylmethylbenzyl)adenine

[0282]

[Chemical formula 92]



The titled compound was prepared in the same method as in Reference Example 2. Yield: 85 %

^{1}H NMR($CDCl_3$)δ 7.30-7.26(2H, m), 7.23-7.21(2H, m), 6.19(2H, brs), 5.32(2H, s), 3.68(3H, s), 3.64(3H, s), 3.61(2H, s), 3.18(2H, t, J = 7.1 Hz), 2.87(2H, t, J = 7.1 Hz).

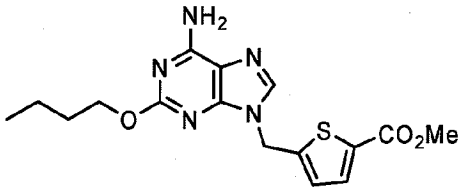
[Example 87]

[0283]

Reference Example 41: Synthesis of 2-butoxy-9-{(5-methoxycarbonyl-2-thienyl)-methyl}adenine

[0284]

[Chemical formula 93]



To a solution of 2-hydroxymethyl-5-methoxycarbonylthiophene (592 mg, 3.44 mmol), triethylamine (Et_3N) (0.70 g, 6.92 mmol) and 4-dimethylamino-pyridine (DMAP) (84 mg, 0.69 mmol) in chloroform (34 ml) was added on an ice bath tosyl chloride (TsCl) (1.31 g, 6.87 mmol), and the mixture was stirred for 1 hour. The reaction solution was poured into a saturated aqueous sodium bicarbonate solution, and the mixture was extracted with dichloromethane. The organic layer was washed with 0.5 N hydrochloric acid and saturated brine, dried over anhydrous magnesium sulfate and concentrated to give the tosylated compound as a yellow oil (1.13 g). 2-Butoxyadenine (0.58 g, 2.84 mmol) and potassium carbonate (238 mg, 1.72 mmol) were added to DMF (40 ml) and the solution was stirred at 60°C for 1 hour. After allowed to cool, thereto was added the tosylated compound, and the mixture was stirred at room temperature for 26 hours, followed by addition of potassium carbonate (238 mg, 1.72 mmol) and stirring at 70°C for 4 hours. After removal of the solvent by evaporation, the residue was poured into water and the mixture was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate and concentrated.

The residue was purified by column chromatography (SiO_2 40 g, elute: $CHCl_3$/ MeOH=100/1) to give the titled compound as a white solid (0.73 g, 2.01 mmol). Yield: 71 %

^{1}H NMR(DMSO-d_6)δ 8.06(1H, s), 7.67(1H, d, J = 3.7 Hz), 7.25(2H, brs), 7.19(1H, d, J = 3.7 Hz), 5.50(2H, s), 4.23(2H, t, J = 6.5 Hz), 3.77(3H, s), 1.66(2H, 5, J = 6.8 Hz), 1.39(2H, 6, J = 7.5 Hz), 0.92(3H, t, J = 7.3Hz).

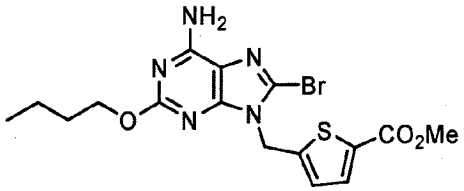
[Example 88]

[0285]

Reference Example 42: Synthesis of 8-bromo-2-butoxy-9-{(5-methoxycarbonyl-2-thienyl)methyl}adenine

[0286]

[Chemical formula 94]



The titled compound was prepared in the same method as in Reference Example 2 as a yellowish white solid. Yield: 90%

^{1}H NMR(DMSO-d_6)δ 7.67(1H, d, J = 3.8 Hz), 7.46(2H, brs), 7.19(1H, d, J = 3.8 Hz), 5.46(2H, s), 4.23(2H, t, J = 6.5 Hz), 3.77(3H, s), 1.67(2H, 5, J = 6.6 Hz), 1.40(2H, 6, J = 7.5 Hz), 0.92(3H, t, J = 7.5 Hz).

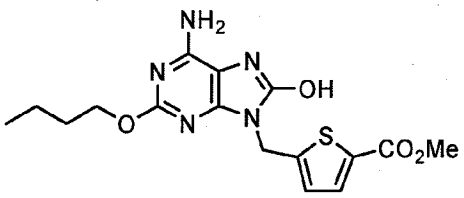
[Example 89]

[0287]

Reference Example 43: Synthesis of 2-butoxy-8-hydroxy-9-{(5-methoxycarbonyl-2-thienyl)methyl}adenine

[0288]

[Chemical formula 95]



The titled compound was prepared in the same method as in Example 4 as a white solid. Yield: 98 % (total of 2 steps)

^{1}H NMR(DMSO-d_6)δ10.11(1H, brs), 7.65(1H, d, J = 3.8 Hz), 7.14(1H, d, J = 3.8 Hz), 6.53(2H, brs), 5.06(2H, s), 4.16(2H, t, J = 6.6 Hz), 3.78(3H, s), 1.63(2H, 5, J = 6.6 Hz), 1.37(2H, 6, J = 7.3 Hz), 0.90(3H, t, J = 7.3 Hz).

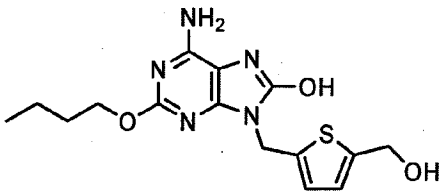
[Example 90]

[0289]

Reference Example 44: Synthesis of 2-butoxy-8-hydroxy-9-{(5-hydroxymethyl-2-thienyl)methyl}adenine

[0290]

[Chemical formula 96]



The titled compound was prepared in the same method as in Reference Example 17 as a white solid. Yield: 95 %

^{1}H NMR(DMSO-d_6)δ 9.98(1H, brs), 6.89(1H, d, J = 3.5 Hz), 6.78(1H, d, J = 3.4 Hz), 6.47(2H, brs), 5.38(1H, t, J = 5.8 Hz), 4.94(2H, s), 4.51(2H, d, J = 5.6 Hz), 4.17(2H, t, J = 6.6 Hz), 1.65(2H, 5, J = 6.6 Hz), 1.38(2H, 6, J = 7.4 Hz), 0.92(3H, t, J = 7.3Hz).

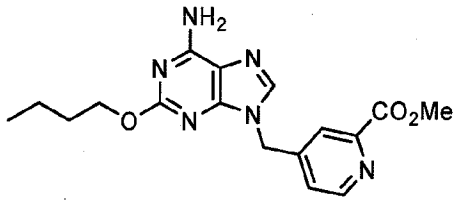
[Example 91]

[0291]

Reference Example 45: Synthesis of 2-butoxy-9-{(2-methoxycarbonyl-4-pyridyl)-methyl}adenine

[0292]

[Chemical formula 97]



The titled compound was prepared in the same method as in Reference Example 1 as a brown oil. Yield: 80 %

^{1}H NMR(DMSO-d_6)δ8.65(1H, dd, J = 0.4, 4.9 Hz), 8.09(1H, s), 7.94(1H, d, J = 0.9 Hz), 7.47(1H, dd, J = 1.5, 4.9 Hz), 7.27(2H, brs), 5.41(2H, s), 4.16(2H, t, J = 6.5 Hz), 3.85(3H, s), 1.60(2H, 5, J = 6.6 Hz), 1.35(2H, 6, J = 7.5 Hz), 0.88(3H, t, J = 7.3 Hz).

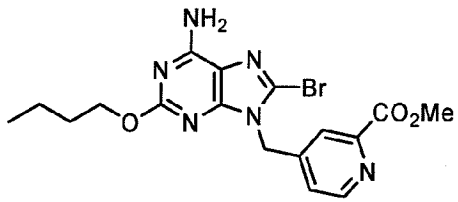
[Example 92]

[0293]

Reference Example 46: Synthesis of 8-bromo-2-butoxy-9-{(2-methoxycarbonyl-4-pyridyl)methyl}adenine

[0294]

[Chemical formula 98]



The titled compound was prepared in the same method as in Reference

Example 2 as a pale yellow oil. Yield: 88 %

^{1}H NMR(DMSO-d_6)δ8.67(1H, dd, J = 0.4, 5.0 Hz), 7.90(1H, d, J = 0.9 Hz), 7.49(2H, brs), 7.38(1H, dd, J = 1.7, 5.0 Hz), 5.40(2H, s), 4.18(2H, t, J = 6.6 Hz), 3.86(3H, s), 1.62(2H, 5, J = 6.6 Hz), 1.35(2H, 6, J = 7.5 Hz), 0.88(3H, t, J = 7.3 Hz).

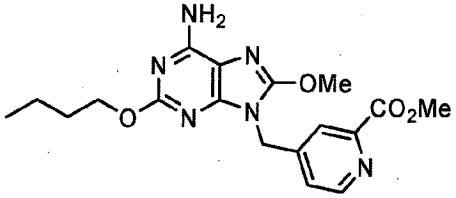
[Example 93]

[0295]

Reference Example 47: Synthesis of 2-butoxy-8-methoxy-9-{(2-methoxycarbonyl-4-pyridyl)methyl}adenine

[0296]

[Chemical formula 99]



8-Bromo-2-butoxy-9-{(2-methoxycarbonyl-4-pyridyl)methyl}adenine (0.75 g, 1.73 mmol) prepared in Reference Example 46 and sodium hydroxide (0.99 g, 24.75 mmol) were suspended in a mixture of water (6 ml) and methanol (6 ml), and the suspension was refluxed for 6 hours. After neutralizing with 12N hydrochloric acid, methanol was removed by evaporation, and the precipitated solid was taken by filtration. The obtained solid was dissolved in a mixture of THF (100 ml) and methanol (10 ml), and thereto was added diazomethane ether solution which was prepared by a conventional method. The solution was stirred at room temperature for 2 hours. After removal of the solvent by evaporation, the residue was purified by column chromatography (SiO_2 50 g, elute: $CHCl_3$/MeOH = 200/0~30/1) to give the titled compound as a white solid (393 mg, 1.01 mmol). Yield: 61 %

^{1}H NMR(DMSO-d_6)δ8.66(1H, d, J = 5.0 Hz), 7.88(1H, d, J = 0.8 Hz), 7.40(1H, dd, J = 1.6, 5.0 Hz), 6.93(2H, brs), 5.19(2H, s), 4.14(2H, t, J = 6.6 Hz), 4.03(3H, s), 3.86(3H, s), 1.60(2H, 5, J = 7.8 Hz), 1.35(2H, 6, J = 7.4 Hz), 0.88(3H, t, J = 7.3 Hz).

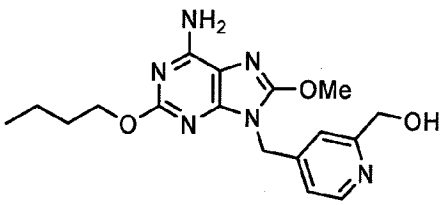
[Example 94]

[0297]

Reference Example 48: Synthesis of 2-butoxy-9-{(2-hydroxymethyl-4-pyridyl)-methyl}-8-methoxyadenine

[0298]

[Chemical formula 100]



The titled compound was prepared in the same method as in Reference Example 17. Yield: 78 %

^{1}H NMR(DMSO-d_6)δ 8.42(1H, d, J = 4.9 Hz), 7.25(1H, s), 7.02(1H, d, J = 3.8 Hz), 6.91(2H, brs), 5.41(1H, t, J = 5.8 Hz), 5.09(2H, s), 4.50(2H, d, J = 5.8 Hz), 4.14(2H, t, J = 6.6 Hz), 3.59(3H, s), 1.61(2H, 5, J = 6.6 Hz), 1.38(2H, 6, J = 7.5 Hz), 0.89(3H, t, J = 7.3 Hz).

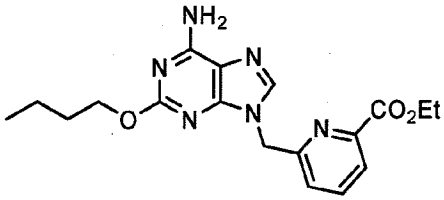
[Example 95]

[0299]

Reference Example 49: Synthesis of 2-butoxy-9-{(6-ethoxycarbonyl-2-pyridyl)-methyl}adenine

[0300]

[Chemical formula 101]



The titled compound was prepared in the same method as in Reference Example 1 as a colorless oil. Yield: 62 %

^{1}H NMR(DMSO-d_6)δ8.06(1H, s), 7.94(2H, m), 7.30(1H, m), 7.26(2H, brs), 5.45(2H, s), 4.34(2H, q, J = 7.1 Hz), 4.12(2H, t, J = 6.6 Hz), 1.57(2H, 5, J = 6.6 Hz), 1.35(5H, m), 0.87(3H, t, J = 7.4 Hz).

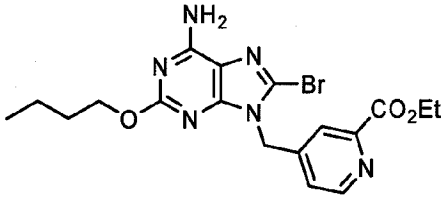
[Example 96]

[0301]

Reference Example 50: Synthesis of 8-bromo-2-butoxy-9-{(6-ethoxycarbonyl-2-pyridyl)methyl}adenine

[0302]

[Chemical formula 102]



The titled compound was prepared in the same method as in Reference Example 2 as a yellowish red solid. Yield: 87 %

^{1}H NMR(DMSO-d_6)δ7.96(2H, m), 7.47(2H, brs), 7.25(1H, m), 5.42(2H, s), 4.32(2H, q, J = 7.1 Hz), 4.13(2H, t, J = 6.6 Hz), 1.58(2H, 5, J = 6.6 Hz), 1.32(5H, m), 0.87(3H, t, J = 7.3 Hz).

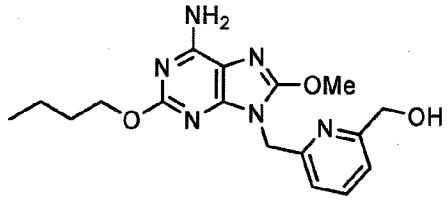
[Example 97]

[0303]

Reference Example 51: Synthesis of 2-butoxy-9-{(6-hydroxymethyl-2-pyridyl)-methyl}-8-methoxyadenine

[0304]

[Chemical formula 103]



Using 8-bromo-2-butoxy-9-{(6-ethoxycarbonyl-2-pyridyl)methyl}adenine prepared in Reference Example 50, the same procedures as in Reference Example 46 and Reference Example 17 were carried out in this order to give the titled compound as a pale yellow oil. Yield: 35 %

^{1}H NMR(DMSO-d_6)δ 7.73(1H, t, J = 7.8 Hz), 7.36(1H, d, J = 7.7 Hz), 6.91(3H, m), 5.40(1H, t, J = 5.8 Hz), 5.10(2H, s), 4.50(2H, d, J = 5.8 Hz), 4.11(2H, t, J = 6.6 Hz), 4.01(3H, s), 1.59(2H, 5, J = 6.6 Hz), 1.35(2H, 6, J = 7.5 Hz), 0.88(3H, t, J = 7.3 Hz).

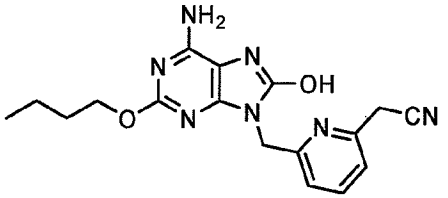
[Example 98]

[0305]

Reference Example 52: Synthesis of 2-butoxy-9-{(6-cyanomethyl-2-pyridyl)-methyl}-8-hydroxyadenine

[0306]

[Chemical formula 104]



To 2-butoxy-9-{(6-hydroxymethyl-2-pyridyl)methyl}-8-methoxyadenine (0.67 mmol) prepared in Reference Example 51 was added thionyl chloride (5 ml) and the solution was refluxed with stirring for 1 hour. After the reaction solution was concentrated, the residue was dissolved in DMF (14 ml) and thereto was added sodium cyanide (164 mg, 3.35 mmol), followed by stirring at room temperature for 18 hours. After removal of the solvent by evaporation, to the residue was added water. After neutralizing with 1N hydrochloric acid, the solution was extracted with chloroform. The extract was dried over anhydrous magnesium sulfate and concentrated. The residue was purified by column chromatography (SiO_2 30 g, elute: $CHCl_3$/MeOH=100/1~30/1) to give the titled compound as a yellowish red solid (133 mg, 0.38 mmol). Yield: 57 %

^{1}H NMR(DMSO-d_6)δ 10.00(1H, s), 7.78(1H, t, J = 7.8 Hz), 7.32(1H, d, J = 7.7 Hz), 7.06(1H, d, J = 7.8 Hz), 6.48(2H, s), 4.96(2H, s), 4.17(2H, s), 4.07(2H, t, J = 6.6 Hz), 1.57(2H, 5, J = 7.8 Hz), 1.32(2H, 6, J = 7.4 Hz), 0.87(3H, t, J = 7.4 Hz).

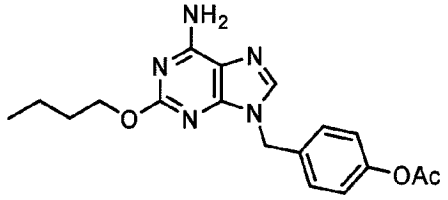
[Example 99]

[0307]

Reference Example 53: Synthesis of 9-(4-acetoxybenzyl)-2-butoxyadenine

[0308]

[Chemical formula 105]



The titled compound was prepared in the same method as in Reference Example 1 as a pale yellow solid. Yield: 56 %

^{1}H NMR(DMSO-d_6)δ8.04(1H, s), 7.34(2H, m), 7.20(2H, brs), 7.09(2H, m), 5.25(2H, s), 4.20(2H, t, J = 6.6 Hz), 1.65(2H, 5, J = 6.6 Hz), 1.39(2H, 6, J = 7.6 Hz), 0.91(3H, t, J = 7.4 Hz).

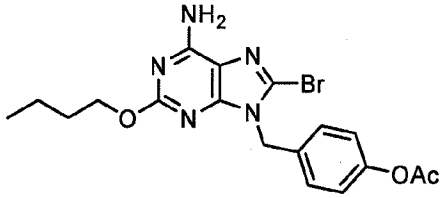
[Example 100]

[0309]

Reference Example 54: Synthesis of 9-(4-acetoxybenzyl)-8-bromo-2-butoxy-adenine

[0310]

[Chemical formula 106]



The titled compound was prepared in the same method as in Reference Example 2 as a yellowish red solid. Yield: 90 %

^{1}H NMR(DMSO-d_6)δ7.39(2H, brs), 7.28(2H, d, J = 8.6 Hz), 7.19(2H, m), 5.25(2H, s), 4.21(2H, t, J = 6.6 Hz), 1.65(2H, 5, J = 6.8 Hz), 1.39(2H, 6, J = 7.6 Hz), 0.91(3H, t, J = 7.2 Hz).

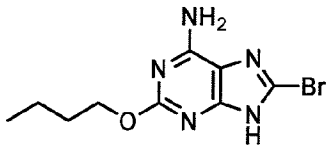
[Example 101]

[0311]

Reference Example 55: Synthesis of 8-bromo-2-butoxyadenine

[0312]

[Chemical formula 107]



9-(4-Acetoxybenzyl)-8-bromo-2-butoxyadenine (1.04 g, 2.39 mmol) prepared in Reference Example 54 was dissolved in a mixture of 1N aqueous sodium hydroxide solution (10 ml) and methanol (10 ml), and the solution was refluxed for 4 hours. After neutralizing with 12N hydrochloric acid, thereto was

added water and the solution was extracted with chloroform. The organic layer was dried over anhydrous magnesium sulfate, concentrated. The residue was purified by column chromatography (SiO_2 100 g, elute: $CHCl_3$/MeOH = 300/1~50/1) to give the titled compound as a pale red solid (0.56 g, 1.94 mmol). Yield: 81 %

^{1}H NMR(DMSO-d_6)δ13.32(1H, brs), 7.23(2H, brs), 5.45(2H, s), 4.15(2H, q, J = 6.8 Hz), 1.64(2H, m), 1.38(2H, m), 0.92(3H, t, J = 7.2 Hz).

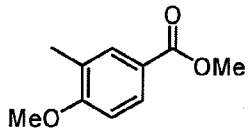
[Example 102]

[0313]

Reference Example 56: Synthesis of methyl 3-methyl-4-methoxybenzoate

[0314]

[Chemical formula 108]



To a solution of 3-methyl-4-methoxybenzoic acid (2.9 g, 17.5 mmol) in methanol (50 ml) was added conc. sulfuric acid (1.5 ml), and the solution was refluxed for 4 hours. After neutralizing with 5 % aqueous sodium bicarbonate solution at 0°C, the precipitated solid was collected by filtration to give the titled compound as a white solid (3.0 g, 16.5 mmol). Yield: 95 %

^{1}H NMR($CDCl_3$)δ 7.89(1H, d, J = 8.6 Hz), 7.83(1H, s), 6.83(1H, d, J = 8.6 Hz), 3.89(3H, s), 3.88(3H, s), 2.34(3H, s).

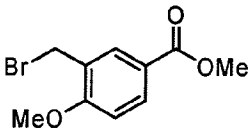
[Example 103]

[0315]

Reference Example 57: Synthesis of methyl 3-bromomethyl-4-methoxybenzoate

[0316]

[Chemical formula 109]



To a solution of methyl 3-methyl-4-methoxybenzoate (3.0 g, 16.5 mmol) prepared in Reference Example 56 in carbon tetrachloride (100 ml) were added N-bromosuccinimide (2.9 g, 16.5 mmol) and benzoyl peroxide (0.10 g), and the mixture was refluxed for 6 hours. After being cooled to 0°C, the precipitate was collected by filtration, and to the filtrate was added a saturated aqueous sodium thiosulfate solution (1 ml). The solution was stirred for 15 minutes and concentrated in vacuo. To the residue was added water and the solution was extracted with chloroform (50 ml×3). The organic layer was concentrated and the precipitated solid was collected by filtration to give the titled compound as a white solid (3.0 g, 11.7 mmol). Yield: 70 %.

^{1}H NMR($CDCl_3$)δ 8.04-7.99(2H, m), 6.91(1H, d, J = 8.6 Hz), 4.55(2H, s), 3.97(3H, s), 3.89(3H, s).

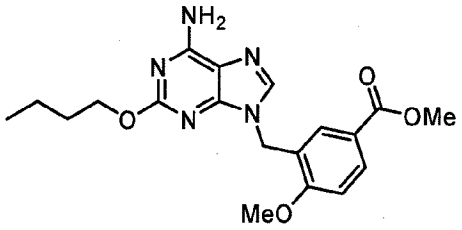
[Example 104]

[0317]

Reference Example 58: Synthesis of 2-butoxy-9-(2-methoxy-5-methoxycarbonyl)-benzyladenine

[0318]

[Chemical formula 110]



The titled compound was prepared in the same method as in Reference Example 1 as a white solid. Yield: 57 %

^{1}H NMR($CDCl_3$)δ 8.09(1H, s), 8.02(1H, d, J = 8.7 Hz), 7.67(1H, s), 6.92(1H, d, J = 8.7 Hz), 5.49(2H, brs), 5.27(2H, s), 4.36(2H, t, J = 6.5 Hz), 3.93(3H, s), 3.87(3H, s), 1.79(2H, tt, J = 7.6 Hz, 6.5 Hz), 1.53(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

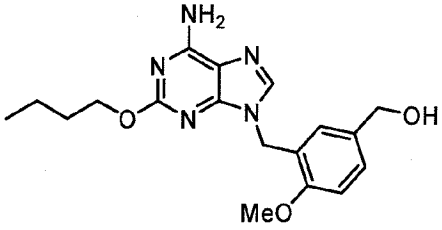
[Example 105]

[0319]

Reference Example 59: Synthesis of 2-butoxy-9-(5-hydroxymethyl-2-methoxy)-benzyladenine

[0320]

[Chemical formula 111]



The titled compound was prepared in the same method as in Reference Example 17 as a white solid. Yield: 88 %

^{1}H NMR(DMSO-d_6)δ 7.88(1H, s), 7.22-7.18(3H, m), 6.99-7.94(2H, m), 5.17(2H, s), 5.05(1H, brs), 4.33(2H, s), 4.19(2H, t, J = 6.6 Hz), 3.83(3H, s), 1.64(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.40(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.91(3H, t, J = 7.4 Hz).

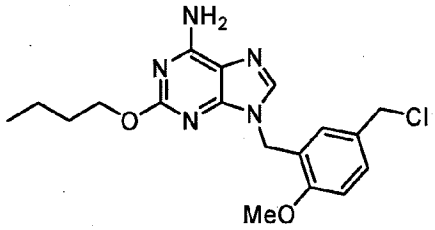
[Example 106]

[0321]

Reference Example 60: Synthesis of 2-butoxy-9-(5-chloromethyl-2-methoxy)-benzyladenine

[0322]

[Chemical formula 112]



The titled compound was prepared in the same method as in Reference Example 18 as a white solid. Yield: 82 %

^{1}H NMR($CDCl_3$)δ 7.69(1H, s), 7.36(1H, s), 7.32(1H, d, J = 8.4 Hz), 6.87(1H, d, J = 8.4 Hz), 5.53(2H, brs), 5.25(2H, s), 4.51(2H, s), 4.36(2H, t, J = 6.6 Hz), 3.88(3H, s), 1.80(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.51(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.98(3H, t, J = 7.4 Hz).

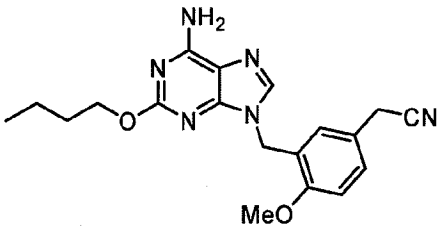
[Example 107]

[0323]

Reference Example 61: Synthesis of 2-butoxy-9-(5-cyanomethyl-2-methoxy)-benzyladenine

[0324]

[Chemical formula 113]



The titled compound was prepared in the same method as in Reference Example 19 as a white solid. Yield: 94 %

^{1}H NMR($CDCl_3$)δ 7.68(1H, s), 7.29-7.22(2H, m), 6.89(1H, d, J = 8.5 Hz), 5.50(2H, brs), 5.25(2H, s), 4.35(2H, t, J = 6.6 Hz), 3.89(3H, s), 3.64(2H, s), 1.81(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.53(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.98(3H, t, J = 7.4 Hz).

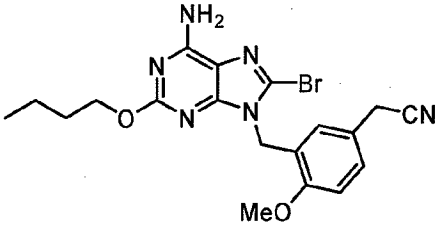
[Example 108]

[0325]

Reference Example 62: Synthesis of 8-bromo-2-butoxy-9-(5-cyanomethyl-2-methoxy)benzyladenine

[0326]

[Chemical formula 114]



The titled compound was prepared in the same method as in Reference Example 2 as a white solid. Yield: 85 %

^{1}H NMR(DMSO-d_6)δ 7.41(2H, brs), 7.26(1H, d, J = 8.5 Hz), 7.08(1H, d, J = 8.5 Hz), 6.67(1H, s), 5.18(2H, s), 4.15(2H, t, J = 6.5 Hz), 3.87(3H, s), 3.86(2H, s), 1.62(2H, tt, J = 7.4 Hz, 6.5 Hz), 1.37(2H, tq, J = 7.4 Hz, 7.4 Hz), 0.88(3H, t, J = 7.4 Hz).

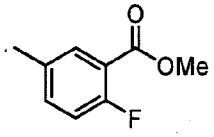
[Example 109]

[0327]

Reference Example 63: Synthesis of methyl 2-fluoro-5-methylbenzoate

[0328]

[Chemical formula 115]



The titled compound was prepared in the same method as in Reference Example 56 as a colorless liquid. Yield: 98 %

^{1}H NMR($CDCl_3$)δ 7.72(1H, dd, J = 6.9, 2.2 Hz), 7.30(1H, m), 7.02(1H, dd, J = 10.6, 8.4 Hz), 3.93(3H, s), 2.35(3H, s).

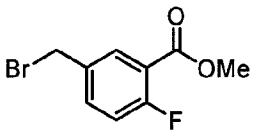
[Example 110]

[0329]

Reference Example 64: Synthesis of methyl 5-bromomethyl-2-fluorobenzoate

[0330]

[Chemical formula 116]



The titled compound was prepared in the same method as in Reference Example 57 as a white solid. Yield: 66 %

^{1}H NMR($CDCl_3$)δ 7.97(1H, dd, J = 6.7, 2.5 Hz), 7.56(1H, m), 7.13(1H, dd, J = 10.3, 8.5 Hz), 4.48(2H, s), 3.94(3H, s).

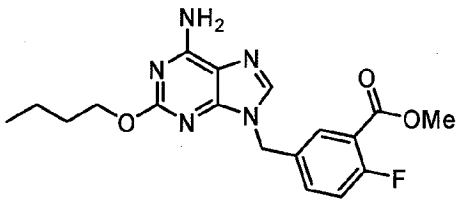
[Example 111]

[0331]

Reference Example 65: Synthesis of 2-butoxy-9-(4-fluoro-3-methoxycarbonyl-benzyl)adenine

[0332]

[Chemical formula 117]



The titled compound was prepared in the same method as in Reference Example 1 as a white solid. Yield: 55 %

^{1}H NMR($CDCl_3$)δ 7.95(1H, dd, J = 6.7, 2.4 Hz), 7.61(1H, s), 7.48(1H, m), 7.12(1H, dd, J = 10.3, 8.6 Hz), 5.55(2H, brs), 5.27(2H, s), 4.33(2H, t, J = 6.6 Hz), 3.93(3H, s), 1.78(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.51(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

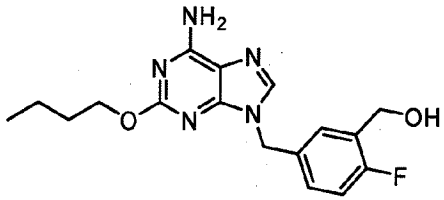
[Example 112]

[0333]

Reference Example 66: Synthesis of 2-butoxy-9-(4-fluoro-3-hydroxymethyl-benzyl)adenine

[0334]

[Chemical formula 118]



The titled compound was prepared in the same method as in Reference Example 17 as a white solid. Yield: 97 %

^{1}H NMR(DMSO-d_6)δ 8.03(1H, s), 7.47(1H, dd, J = 7.1, 2.2 Hz), 7.28(1H, m), 7.11(1H, dd, J = 10.2, 8.6 Hz), 5.23(2H, s), 4.49(2H, s), 4.21(2H, t, J = 6.6 Hz), 1.65(2H, tt, J = 7.5 Hz, 6.6 Hz), 1.38(2H, tq, J = 7.5 Hz, 7.4 Hz), 0.91(3H, t, J = 7.4 Hz).

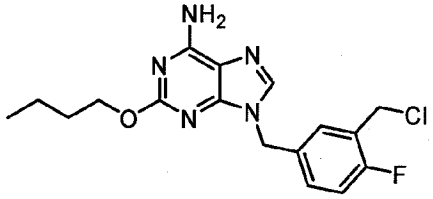
[Example 113]

[0335]

Reference Example 67: Synthesis of 2-butoxy-9-(3-chloromethyl-4-fluorobenzyl)-adenine

[0336]

[Chemical formula 119]



The titled compound was prepared in the same method as in Reference Example 18 as a pale yellow solid. Yield: 95 %

^{1}H NMR($CDCl_3$)δ 7.61(1H, s), 7.40(1H, dd, J = 6.9, 2.2 Hz), 7.25(1H, m), 7.05(1H, dd, J = 9.0, 8.8 Hz), 5.84(2H, brs), 5.25(2H, s), 4.59(2H, s), 4.33(2H, t, J = 6.6 Hz), 1.78(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.50(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

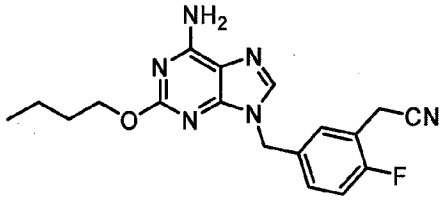
[Example 114]

[0337]

Reference Example 68: Synthesis of 2-butoxy-9-(3-cyanomethyl-4-fluorobenzyl)-adenine

[0338]

[Chemical formula 120]



The titled compound was prepared in the same method as in Reference Example 19 as a white solid. Yield: 88 %

^{1}H NMR($CDCl_3$)δ 7.61(1H, s), 7.44(1H, dd, J = 7.0, 2.1 Hz), 7.29(1H, m), 7.08(1H, dd, J = 9.0, 8.8 Hz), 5.54(2H, brs), 5.26(2H, s), 4.34(2H, t, J = 6.6 Hz), 3.75(2H, s), 1.79(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.51(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

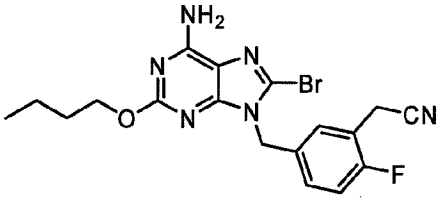
[Example 115]

[0339]

Reference Example 69: Synthesis of 8-bromo-2-butoxy-9-(3-cyanomethyl-4-fluorobenzyl)adenine

[0340]

[Chemical formula 121]



The titled compound was prepared in the same method as in Reference Example 2 as a white solid. Yield: 77 %

^{1}H NMR($CDCl_3$)δ 7.53(1H, dd, J = 7.0, 2.1 Hz), 7.34(1H, m), 7.06(1H, dd, J = 9.0, 8.8 Hz), 6.01(2H, brs), 5.28(2H, s), 4.34(2H, t, J = 6.6 Hz), 3.75(2H, s), 1.77(2H, tt, J = 7.6 Hz, 6.6 Hz), 1.51(2H, tq, J = 7.6 Hz, 7.4 Hz), 0.97(3H, t, J = 7.4 Hz).

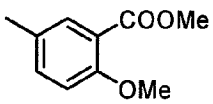
[Example 116]

[0341]

Reference Example 70: Synthesis of methyl 2-methoxy-5-methylbenzoate

[0342]

[Chemical formula 122]



The titled compound was prepared in the same method as in Reference Example 13. Yield: 88 %

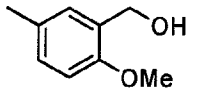
[Example 117]

[0343]

Reference Example 71: Synthesis of 2-methoxy-5-methylbenzyl alcohol

[0344]

[Chemical formula 123]



The titled compound was prepared in the same method as in Reference Example 17. Yield: 82 %

^{1}H NMR($CDCl_3$)δ 7.06(1H, s), 7.04(1H, d, J = 8.3 Hz), 6.76(1H, d, J = 8.3 Hz), 4.63(2H, s), 3.81(3H, s), 2.26(3H, s).

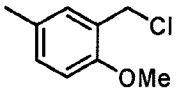
[Example 118]

[0345]

Reference Example 72: Synthesis of 2-methoxy-5-methylbenzyl chloride

[0346]

[Chemical formula 124]



The titled compound was prepared in the same method as in Reference Example 18. Yield: 100 %

^{1}H NMR($CDCl_3$)δ 7.14(1H, s), 7.08(1H, d, J = 8.3 Hz), 6.76(1H, d, J = 8.3 Hz), 4.61(2H, s), 3.831(3H, s), 2.26(3H, s).

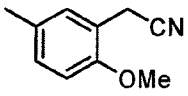
[Example 119]

[0347]

Reference Example 73: Synthesis of 2-methoxy-5-methylphenylacetonitrile

[0348]

[Chemical formula 125]



The titled compound was prepared in the same method as in Reference Example 19. Yield: 73 %

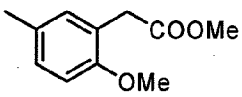
[Example 120]

[0349]

Reference Example 74: Synthesis of methyl 2-methoxy-5-methylphenylacetate

[0350]

[Chemical formula 126]



The titled compound was prepared in the same method as in Reference

Example 20. Yield: 73 %

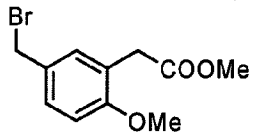
[Example 121]

[0351]

Reference Example 75: Synthesis of methyl 3-bromomethyl-6-methoxyphenyl-acetate

[0352]

[Chemical formula 127]



The titled compound was prepared in the same method as in Reference Example 57. Yield: 70 %

[Example 122]

[0353]

Example of Pharmaceutical Formulation

An aerosol solution is prepared wherein the following components are contained per 1 g of the solution.

Compound of Example 1:	0.641 mg (0.06 %)
Ethanol:	26.816 mg (2.68 %)
1,1,1,2-Tetrafluoroethane:	972.543 mg (97.25 %)

[Example 123]

[0354]

Example of Pharmaceutical Formulation

An aerosol solution is prepared wherein the following components are contained per 1 g of the solution.

Compound of Example 15:	0.641 mg (0.06 %)
Ethanol:	26.816 mg (2.68 %)
1,1,1,2-Tetrafluoroethane:	972.543 mg (97.25 %)

[Document Name] Abstract

[Abstract]

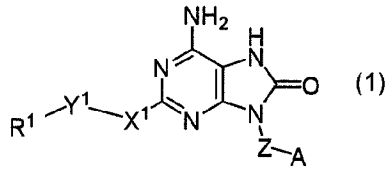
[Object]

An object of the present invention is to provide an immuno-modulator having specific activity against Th1/Th2, more particularly, to provide a medicament for topical application which can be used in the treatment or prevention of allergic diseases, virus diseases or cancers.

[Means for solution]

An 8-oxoadenine compound of the formula (1):

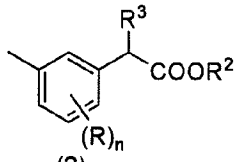
[Chemical formula 1]



(1)

[wherein "-A" is a group of the following formula (2):

[Chemical formula 1]



(2)

(wherein R^2 is an optionally substituted alkyl; R^3 is H or alkyl; R is halogen, haloalkyl, alkyl, etc.; n is an integer of 0 to 2), etc.; X^1 is oxygen, sulfur, single bond, etc.; Y^1 is single bond or a straight or branched alkylene; Z is straight or branched alkylene; R^1 is H, hydroxy, alkoxy, alkoxycarbonyl, etc.]

or a pharmaceutically acceptable salt thereof.

[Selected figure] Nil